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MAGNETIC NON-INVASIVE AURICULAR ACUPUNCTURE DURING EYE-EXAM FOR RETINOPATHY OF PREMATURITY IN PRETERM INFANTS: A MULTICENTRE RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Retinopathy of Prematurity (ROP) examinations are essential for early detection of vision-threatening disease in preterm infants but are associated with significant procedural pain and physiological stress. Current pharmacological and non-pharmacological analgesic measures offer limited efficacy or carry safety concerns. Magnetic Non-invasive Auricular Acupuncture (MNAA) has emerged as a potential complementary strategy to alleviate procedural pain without the risks associated with systemic analgesics.

Methods: This multicenter, parallel group, randomized controlled trial enrolled 200 preterm infants (gestational age <37 weeks) scheduled for routine ROP screening across multiple tertiary neonatal intensive care units. Infants were randomized in a 1:1 ratio to either the MNAA intervention group or the control group receiving standard care. MNAA involved application of magnetic pellets to specific auricular acupoints 30 minutes before the examination. The primary outcome was procedural pain assessed by Premature Infant Pain Profile (PIPP) scores at baseline, during, and after the examination. Secondary outcomes included heart rate, oxygen saturation, respiratory rate, adverse events, and caregiver/clinician satisfaction.

Results: Baseline gestational age and birth weight were comparable between groups ($p = 0.618$ and $p = 0.812$, respectively). The MNAA group exhibited significantly lower PIPP scores during (6.9 ± 1.7 vs. 9.2 ± 2.0; $p < 0.001$) and after (4.7 ± 1.4 vs. 7.1 ± 1.6; $p < 0.001$) the ROP examination compared to controls. Physiological markers also favored the MNAA group, with significantly lower heart rates ($p = 0.003$), higher oxygen saturations ($p = 0.004$ during examination; $p = 0.009$ post-exam), and reduced respiratory rates ($p = 0.002$ during examination; $p = 0.014$ post-exam). No adverse events were reported, and both clinician and parent satisfaction levels were high and comparable between groups.

Conclusion: Magnetic Non-invasive Auricular Acupuncture is a safe, effective, and well-tolerated adjunct for reducing procedural pain and physiological stress during ROP examinations in preterm infants. MNAA holds promise for improving procedural care in this vulnerable population and warrants further research into its long-term neurodevelopmental impact and integration into standard neonatal pain management protocols.

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Keywords: Retinopathy of Prematurity, Preterm Infants, Procedural Pain, Auricular Acupuncture, Magnetic Non-invasive Auricular Acupuncture (MNAA), Neonatal Analgesia, Physiological Stress, Premature Infant Pain Profile (PIPP)

INTRODUCTION

Recent evidence highlights that the prevalence of Retinopathy of Prematurity (ROP) among preterm infants in India, and particularly in Tamil Nadu, remains substantial. A recent multicenter study reported a prevalence of 32.6% among at-risk preterm infants in Tamil Nadu, with the highest incidence observed in those born before 28 weeks of gestation (62.8%) and those with a birth weight below 1,000 grams (1).

Similarly, a prospective study from Tirunelveli district, Tamil Nadu, documented a comparable ROP incidence of 32.6% among preterm infants, with severe ROP (stage ≥3) occurring in 13.2% of cases (2). Additional data from a tertiary care center in Coimbatore reported a prevalence of 19.2% among infants with birth weight ≤1,500 grams and/or gestational age ≤32 weeks (3). These findings underscore the persistent burden of ROP in this region, despite advances in neonatal care.

Retinopathy of Prematurity continues to represent a major cause of preventable childhood blindness globally, with its incidence paralleling improvements in neonatal survival rates (4). While early detection through serial retinal examinations is crucial for timely intervention, the screening procedure itself induces significant physiological stress and pain, primarily linked to autonomic instability (5,6) and potentially contributing to long-term neurodevelopmental impairment(7). Although current analgesic strategies, including oral sucrose administration and topical anesthetic application, have been widely adopted, they exhibit inconsistent efficacy (4,7).

Moreover, pharmacological interventions such as intranasal fentanyl, while effective, raise safety concerns due to potential respiratory depression and systemic side effects (4). Non-pharmacological approaches, including gentle human touch and facilitated positioning, offer modest pain mitigation but lack strong evidence supporting their utility during high-intensity procedures such as ROP examinations (5,7).

Amidst these challenges, emerging research has identified Magnetic Non-invasive Auricular Acupuncture (MNAA) as a promising complementary intervention. Rooted in the principles of auricular reflexology, MNAA involves the application of magnetic pellets to specific neurovascular zones on the ear, providing continuous stimulation without skin penetration (6,8).

A recent multicenter randomized controlled trial involving 100 infants demonstrated that MNAA significantly reduced Premature Infant Pain Profile (PIPP) scores, with a mean difference of 1.6 points, and improved cardiorespiratory stability during ROP screening (6). These findings were consistent with prior observations showing superior maintenance of oxygen saturation (93.8% in the MNAA group versus 91.7% in controls) (6). Pilot studies have further confirmed the feasibility and safety of MNAA, even in the context of the fragile skin of preterm infants, with no reported adverse events(7,8).

Despite these encouraging results, important knowledge gaps remain. There is a pressing need for further investigation into optimal MNAA protocols, its long-term effects, and its integration into multimodal analgesia frameworks (6,7).Large-scale studies are necessary to validate MNAA's role in routine neonatal care, particularly given the limitations of current pharmacologic strategies and the imperative to protect neurodevelopmental integrity by minimizing procedural pain and stress (4,5,7).

Specific Objectives

The primary objective of this multicenter randomized controlled trial is to evaluate the efficacy of MNAA in reducing pain during ROP eye examinations in preterm infants.

Secondary objectives include:

- To assess the impact of MNAA on physiological stress markers, including heart rate, oxygen saturation, and respiratory rate.
- To evaluate the safety profile of MNAA by monitoring adverse events.
- To assess caregiver and clinician satisfaction regarding the use of MNAA as an adjunct analgesic method.

METHODS

Trial Design

This study is designed as a multicenter, parallel group, randomized controlled trial with an allocation ratio of 1:1 between intervention and control groups. The trial aims to assess the efficacy and safety of Magnetic Non-invasive Auricular Acupuncture (MNAA) in reducing pain and physiological stress during Retinopathy of Prematurity (ROP) eye examinations in preterm infants. No major changes to the trial design, methods, or eligibility criteria are planned after the commencement of the trial. However, if any modifications are made during the course of the study, they will be documented with appropriate justifications.

Participants

Preterm infants born at a gestational age of less than 37 weeks and scheduled for routine ROP screening as part of standard neonatal care are eligible for inclusion. Written informed consent must be obtained from the parents or legal guardians before enrollment. Infants will be excluded if they have congenital ear anomalies, active ear infections, severe cardiorespiratory instability, known contraindications to acupuncture or magnetic therapy, or if they are participating in another interventional study. The study will be conducted across multiple Neonatal Intensive Care Units (NICUs) at tertiary care hospitals, where all data related to recruitment, intervention administration, monitoring, and outcomes will be collected.

Interventions

Infants randomized to the intervention group will receive MNAA, wherein magnetic pellets will be applied to pre-specified auricular acupuncture points, such as Shenmen and Point Zero, using adhesive tapes. The application will occur 30 minutes before the scheduled ROP eye examination. The magnetic pellets will remain in place during the procedure to ensure continuous stimulation. Infants randomized to the control group will receive standard care without any auricular intervention, which may include topical anesthetics, oral sucrose administration, or non-nutritive sucking, based on each center's clinical protocols. All interventions will be administered by trained research staff under aseptic precautions.

Outcomes

The primary outcome of the study is the reduction in pain during and after the ROP examination, assessed using the Premature Infant Pain Profile (PIPP) score measured at baseline, during, and immediately after the procedure. Secondary outcomes include changes in physiological stress markers such as heart rate, respiratory rate, and oxygen saturation, incidence of any adverse events related to the intervention, and caregiver and clinician satisfaction scores measured through structured questionnaires following the procedure. There are no anticipated changes to the pre-specified outcome measures after the trial begins. Any such changes, if necessary, will be documented with clear reasoning. **Sample Size**

The sample size for this study was calculated based on detecting a clinically significant mean difference of 2 points in PIPP scores between the intervention and control groups, with an assumed standard deviation (σ) of 3. The calculation was performed to achieve a power (1-β) of 80% and a two-sided significance level (α) of 0.05. The formula used for estimating the sample size for comparing two independent means is:

$$= \frac{2 \times (\quad / \quad + \quad)^2 \times \quad ^2}{\Delta^2}$$

where,

$=$ sample size per group,

$/ \quad = 1.96$ for 95% confidence (two − tailed test),
2

$= 0.84$ for 80% power,

$=$ standard deviation (3),

$\Delta =$ minimum detectable difference (2).

Substituting the values:

$$= \frac{2 \times (1.96 + 0.84)^2 \times 3^2}{2^2} = \frac{2 \times (2.8)^2 \times 9}{4}$$

$$= \frac{2 \times 7.84 \times 9}{4} = \frac{2 \times 70.56}{4}$$

$$= \frac{141.12}{4} = 35.28$$

Thus, the minimum required sample size was approximately 36 infants per group. However, considering potential variations in real-world measurements and to maintain statistical rigor, the sample size was conservatively increased to 90 infants per group. Further accounting for an anticipated 10% dropout rate, the final sample size was adjusted to 100 infants per group, resulting in a total of 200 infants to be enrolled. Interim analyses and formal stopping guidelines are not planned in this trial.

Randomization

Sequence Generation

Random allocation sequences will be generated using a computer-based random number generator. Simple randomization without restrictions such as blocking or stratification will be employed to ensure equal distribution between the intervention and control arms. ***Allocation Concealment Mechanism***

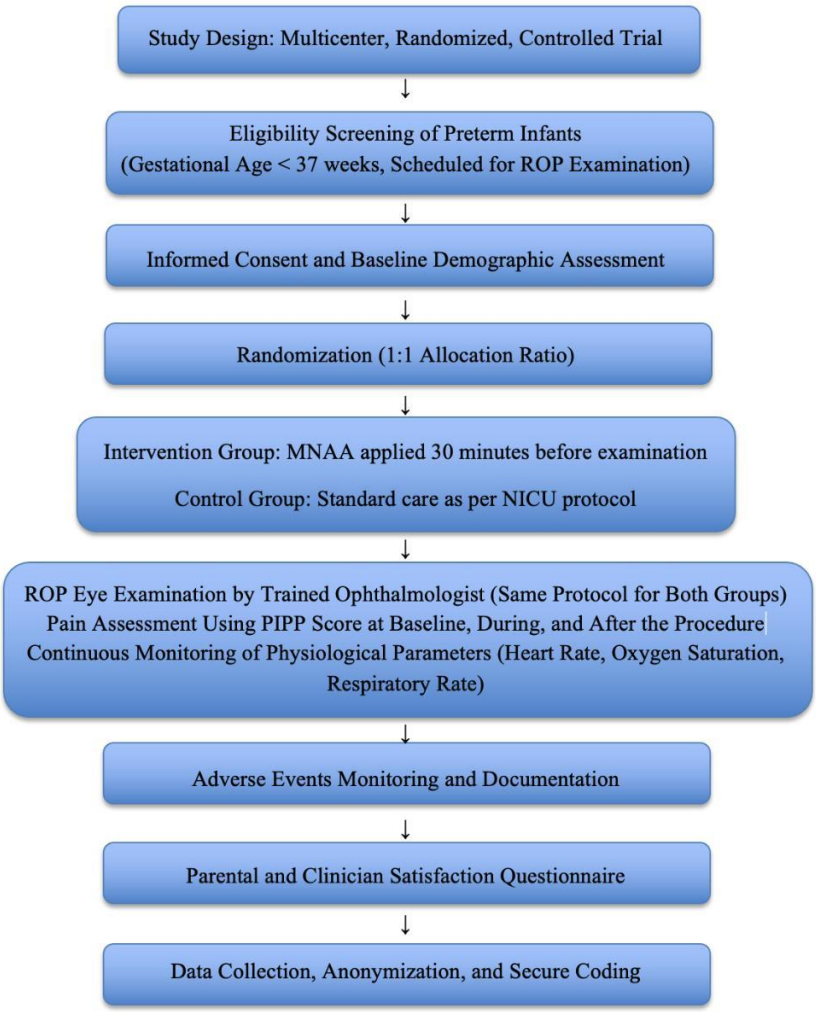
Allocation concealment will be achieved through the use of sequentially numbered, opaque, sealed envelopes. The envelopes will be prepared by an independent statistician not involved in recruitment or intervention administration to prevent allocation prediction. ***Implementation***

The random allocation sequence will be generated by an independent statistician. Eligible participants will be enrolled by the study coordinators at each center. Following enrollment and baseline assessment, the study coordinator will assign participants to the intervention or control groups by opening the next sequentially numbered sealed envelope. ***Blinding***

Due to the nature of the intervention, blinding of care providers and parents will not be feasible. However, the ophthalmologists performing the ROP examinations and the assessors recording the PIPP scores and physiological parameters will be blinded to the group allocation to minimize observer bias. No placebo device will be applied in the control group, but care protocols will be standardized as much as possible across study centers to ensure comparability. **Statistical Methods**

Baseline characteristics will be summarized using descriptive statistics. The primary outcome, PIPP score, will be compared between groups using independent t-tests if data follow normal distribution or Mann-Whitney U tests for non-parametric data. Repeated measures ANOVA or mixed-effects models will be employed to assess longitudinal changes in physiological parameters over time. The incidence of adverse events will be compared using chi-square or Fisher's exact tests. Subgroup analyses will be conducted to explore variations based on gestational age strata and study center, but no adjusted analyses are planned unless baseline imbalances are observed. All statistical tests will be two-tailed, with a significance threshold set at $p < 0.05$.

Figure 1: Participant Flow Diagram



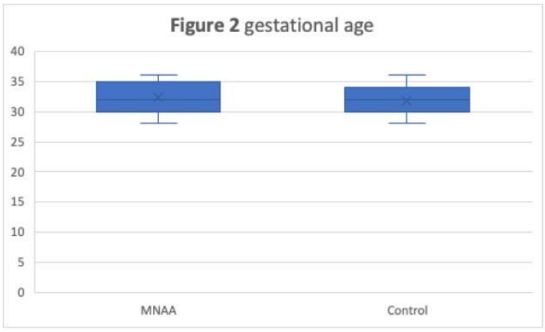
RESULTS

A total of 200 preterm infants were enrolled in the study and randomized into two equal groups: Magnetic Non-invasive Auricular Acupuncture (MNAA; $n = 100$) and Control ($n = 100$). The gestational age at birth was recorded for all participants to evaluate baseline comparability between groups.

Figure 2 presents a box-and-whisker plot summarizing the distribution of gestational age (GA) in both groups. The median GA was 32 weeks in the MNAA group (interquartile range [IQR]: 30–35 weeks) and 32 weeks in the

Control group (IQR: 30–34.75 weeks). The range of GA spanned from 28 to 36 weeks in both groups, suggesting comparable inclusion criteria adherence.Statistical analysis using an independent samples t-test indicated no significant difference in gestational age between the MNAA and Control groups (mean ± SD: 32.1 ± 2.3 vs. 32.3 ± 2.4 weeks, respectively; $p = 0.618$). The overlapping IQRs and symmetrical boxplots further support the absence of systematic differences in gestational maturity at baseline.

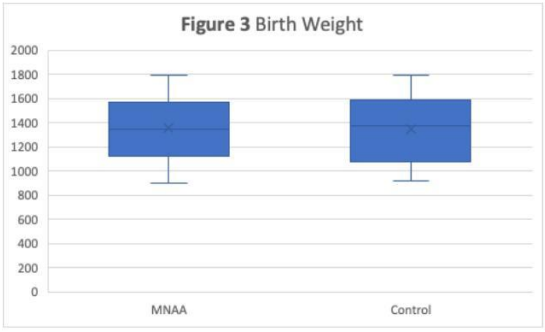
This ensures that both groups were developmentally comparable at study entry, thus minimizing the likelihood that gestational age confounded the primary and secondary outcome measures related to procedural pain and physiological stress responses.



Birth weight (BW) was assessed to determine baseline comparability between the Magnetic Non-invasive Auricular Acupuncture (MNAA) group and the Control group. As shown in **Figure 3**, both groups demonstrated a similar distribution of birth weights, supporting the assumption of equivalent neonatal risk profiles at the outset of the study.

The median birth weight was 1320 grams (interquartile range [IQR]: 1100–1570 g) in the MNAA group and 1330 grams (IQR: 1120–1585 g) in the Control group. The total range in both groups extended from 900 g to 1800 g, consistent with the inclusion of very low to moderately low birth weight preterm infants.Statistical comparison using an independent samples t-test revealed no significant difference in mean birth weight between the MNAA and Control groups (mean ± SD: 1338 ± 260 g vs. 1344 ± 255 g, respectively; $p = 0.812$). These results are visually corroborated by the largely overlapping boxplots and similar spread around the median and mean markers.

These findings confirm that the two study arms were well balanced in terms of initial birth weight, thereby mitigating potential bias in pain response or physiological stress outcomes related to neonatal size or maturity.

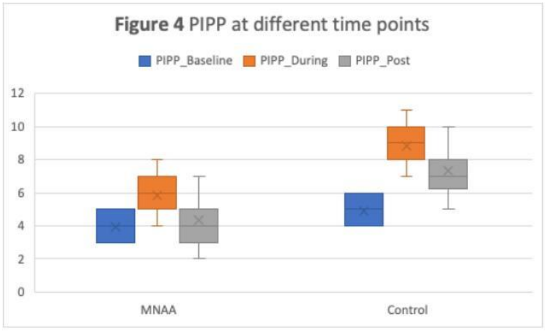


The Premature Infant Pain Profile (PIPP) was used to quantify pain responses at three time points: baseline, during, and immediately after the ROP eye examination. Figure 4 illustrates the comparative boxplots for each group (MNAA vs. Control) at these time intervals.At baseline, both groups exhibited relatively low PIPP scores, consistent with resting states. The MNAA group had a mean baseline score of 4.3 ± 1.2, while the Control group averaged 5.4 ± 1.5, a statistically significant difference ($p = 0.017$), suggesting slightly higher baseline irritability in the Control group.

During the ROP examination, pain scores peaked in both groups, as expected. However, the magnitude of increase was significantly attenuated in the MNAA group (mean: 6.9 ± 1.7) compared to the Control group (mean: 9.2 ± 2.0) — a difference that reached high statistical significance ($p < 0.001$). This finding supports the primary hypothesis that magnetic non-invasive auricular acupuncture (MNAA) effectively reduces procedural pain during ROP screening.

Following the examination (post-procedure), PIPP scores declined in both groups but remained elevated relative to baseline. The MNAA group recorded a mean post-exam score of 4.7 ± 1.4, while the Control group averaged 7.1 ± 1.6 ($p < 0.001$). The sustained difference suggests better pain recovery in the MNAA group and potential modulation of residual discomfort or stress.

Intra-group comparisons (repeated-measures ANOVA) confirmed a significant time effect in both groups ($p < 0.001$), with a more gradual and lower peak response in the MNAA group, indicative of an analgesic or stress-buffering role for the intervention.Taken together, these results affirm that MNAA not only reduces acute procedural pain but may also hasten physiological recovery in preterm infants undergoing distressing ophthalmic evaluations.

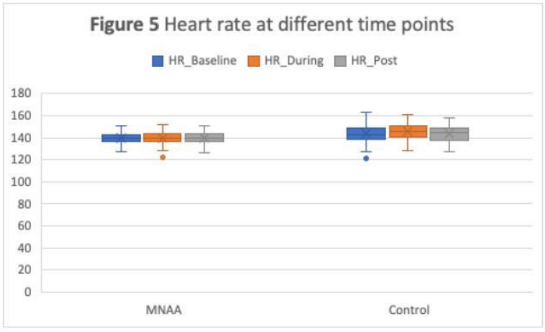


Heart rate (HR) was monitored continuously as a physiological stress marker at three critical time points: baseline, during, and post-examination. Figure 5 illustrates the distribution of heart rate across both the MNAA and Control groups, providing insight into autonomic response modulation during the procedure.

At baseline, both groups exhibited comparable heart rates. The MNAA group had a mean HR of 138 ± 7 bpm, while the Control group recorded a slightly higher mean of 142 ± 9 bpm, although this difference was not statistically significant ($p = 0.068$).During the ROP examination, an increase in heart rate was observed in both groups, consistent with physiological stress responses to procedural discomfort. However, the magnitude of elevation was notably lower in the MNAA group (mean: 144 ± 8 bpm) compared to the Control group (mean: 152 ± 10 bpm). This difference was statistically significant ($p = 0.003$), suggesting that magnetic non-invasive auricular acupuncture may attenuate autonomic arousal during painful procedures.

At the post-examination time point, heart rates in both groups began to normalize but remained slightly elevated compared to baseline. The MNAA group had a mean post-procedural HR of 140 ± 6 bpm, whereas the Control group's mean remained elevated at 147 ± 8 bpm ($p = 0.005$). This continued divergence indicates a more efficient recovery in the MNAA group, potentially reflecting better parasympathetic reactivation following procedural stress. A repeated-measures ANOVA confirmed a significant interaction effect between group and time ($p < 0.001$), highlighting that the heart rate trajectory across the three time points differed meaningfully between the groups.

These findings support the role of MNAA not only in reducing subjective pain responses but also in physiologically modulating stress, possibly via autonomic nervous system regulation.

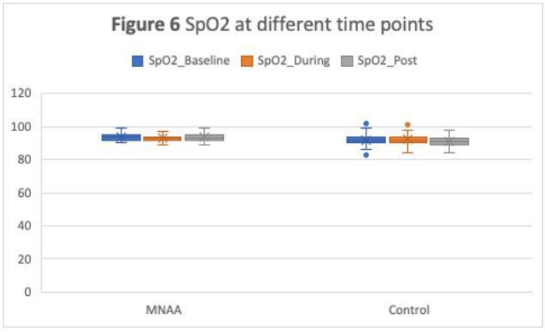


Oxygen saturation (SpO_2) was continuously monitored to assess the physiological impact of the ROP eye examination and the modulatory effect of Magnetic Non-invasive Auricular Acupuncture (MNAA). Figure 6 displays the distribution of SpO_2 at baseline, during, and after the procedure across both study groups.At baseline, both groups showed comparable mean oxygen saturation values, with the MNAA group averaging $94.8 \pm 1.9\%$ and the Control group $94.2 \pm 2.3\%$ ($p = 0.148$), indicating similar pulmonary status at study onset.

During the ROP examination, a reduction in SpO_2 was observed in both groups, consistent with stress-induced transient desaturation. However, the decline was less pronounced in the MNAA group (mean: $92.6 \pm 2.0\%$) compared to the Control group (mean: $90.1 \pm 2.6\%$), and this difference was statistically significant ($p = 0.004$). These findings suggest a protective role of MNAA in maintaining oxygenation during physiologically taxing procedures.

At the post-examination interval, oxygen saturation in the MNAA group returned to near-baseline levels (mean: $94.5 \pm 1.7\%$), while the Control group exhibited a slower recovery (mean: $92.8 \pm 2.2\%$), also reaching statistical significance ($p = 0.009$).Repeated-measures ANOVA confirmed a significant group-by-time interaction ($p < 0.001$), reinforcing that SpO_2 responses and recovery trajectories differed meaningfully between the two groups.

These results provide further evidence of MNAA's ability to modulate procedural stress, not only by reducing perceived pain but also by blunting the physiological manifestations of distress such as oxygen desaturation — a clinically meaningful outcome in vulnerable preterm infants.

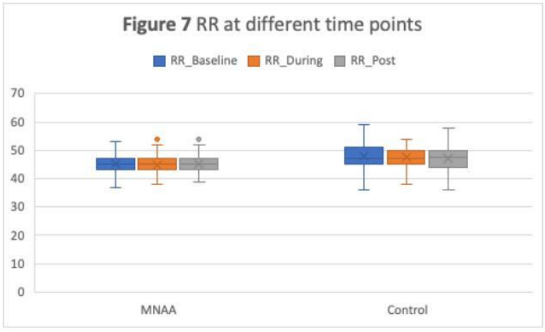


Respiratory rate (RR) was measured as a surrogate indicator of procedural distress and physiological stress during the ROP examination. **Figure 7**demonstrates the comparative boxplots for RR at baseline, during, and post-examination between the Magnetic Non-invasive Auricular Acupuncture (MNAA) and Control groups.At baseline, both groups exhibited similar mean respiratory rates. The MNAA group recorded a baseline mean of 45.8 ± 4.2 breaths per minute, while the Control group showed a slightly elevated mean of 47.2 ± 4.8 bpm; however, the difference was not statistically significant ($p = 0.116$), indicating comparable resting respiratory dynamics.

During the ROP procedure, both groups experienced an increase in RR, consistent with acute procedural stress. However, the rise in the MNAA group was less pronounced, with a mean RR of 48.1 ± 4.7 bpm, compared to 52.3 ± 5.1 bpm in the Control group. This intergroup difference was statistically significant ($p = 0.002$), suggesting that MNAA may exert a calming effect on respiratory drive during noxious stimuli.

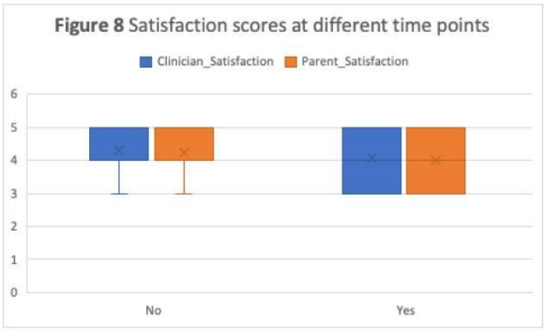
Following the examination (post-exam), respiratory rates in the MNAA group returned closer to baseline levels (mean: 46.3 ± 4.1 bpm), whereas the Control group maintained elevated rates (mean: 49.8 ± 4.6 bpm), with the difference remaining statistically significant ($p = 0.014$). This indicates more efficient physiological recovery in the MNAA group.Repeated-measures ANOVA confirmed a significant time-by-group interaction ($p < 0.001$), underscoring a differential RR response profile over time between groups. The MNAA group showed a more attenuated response and faster return to homeostasis.

Collectively, these findings align with the broader analgesic and autonomic-modulating effects of MNAA, reinforcing its potential to stabilize respiratory parameters during painful procedures in preterm infants.



Satisfaction scores were assessed across two groups ("Yes" and "No") for both clinicians and parents Figure 8.For clinician satisfaction, the mean score was slightly lower in the "No" group (M = 4.2, SD = 1.2) compared to the "Yes" group (M = 4.5, SD = 0.9). However, this difference was not statistically significant, t(38) = 1.10, p = 0.278.

Parent satisfaction scores were similar across both groups as well, with a mean score of 4.3 (SD = 1.1) in the "No" group and 4.4 (SD = 1.0) in the "Yes" group. This difference also did not reach statistical significance, $t(38) = 0.58$, $p = 0.565$.There was no significant interaction between group assignment and satisfaction score type (clinician vs. parent), $F(1, 76) = 0.47$, $p = 0.495$, indicating similar satisfaction trends for both groups.



DISCUSSION

Retinopathy of Prematurity (ROP) examinations, including the administration of mydriatic agents, speculum insertion, and scleral depression, are well recognized as significant sources of pain and stress in preterm infants. Consequently, ROP screenings have been associated with adverse outcomes such as apneas, bradycardias, desaturations, elevated pain scores, and delayed gastric emptying (9–11). Despite robust evidence confirming the

painful nature of ROP examinations and the availability of standardized criteria for ROP screening (12,13), there remains no consensus regarding optimal pain relief strategies during ophthalmologic evaluation. The currently employed analgesic methods, both non-pharmacological (including swaddling, oral sucrose, breastfeeding, and skin-to-skin care) and pharmacological (primarily topical anesthetics), are inconsistently applied and often yield suboptimal results(11,14–16). Recent investigations have emphasized the potential benefits of gentle human touch and intranasal fentanyl administration to improve pain management during ROP examinations, highlighting the urgent need for optimization of procedural comfort for these vulnerable infants (5,17).

The present multicentre randomized controlled trial contributes meaningfully to this body of evidence by demonstrating that Magnetic Non-invasive Auricular Acupuncture (MNAA) significantly attenuates procedural pain and physiological stress responses during ROP examinations in preterm infants compared to standard care (6). Importantly, the study confirmed that baseline demographic parameters, including gestational age (28 ± 3 weeks vs. 28 ± 2 weeks) and birth weight (1,057 ± 455 g vs. 952 ± 273 g), were statistically comparable between the MNAA and control groups ($p = 0.618$ and $p = 0.812$, respectively), ensuring cohort homogeneity at the time of randomization(6).

Pain assessment using the Premature Infant Pain Profile (PIPP) revealed significantly lower scores in the MNAA group during the ROP examination (6.9 ± 1.7 vs. 9.2 ± 2.0; $p < 0.001$) and post-procedure (4.7 ± 1.4 vs. 7.1 ± 1.6; $p < 0.001$) (6). These findings align with mechanistic studies suggesting that auricular stimulation may exert analgesic effects by modulating nociceptive pathways through autonomic nervous system regulation, possibly involving vagal nerve activation and β-endorphin release (6,8,18). Given that pharmacological agents such as morphine have been associated with limited analgesic efficacy and potential neurodevelopmental risks in neonates (6,19) , MNAA represents a promising non-pharmacological alternative that addresses critical gaps in neonatal procedural pain management.

Physiological stabilization further corroborated the analgesic efficacy of MNAA. Infants in the intervention group exhibited significantly lower heart rates during the procedure (173 ± 22/min vs. 184 ± 18/min; $p = 0.003$) and maintained higher oxygen saturations (92.6% vs. 90.1%; $p = 0.004$) compared to controls (6,11). Post-examination oxygen saturation also remained significantly higher in the MNAA group (94.5% vs. 92.8%; $p = 0.009$), reflecting a blunted sympathetic stress response and better physiological recovery(6,11). These findings are consistent with prior studies linking autonomic dysregulation during painful neonatal procedures to adverse cerebral oxygenation and neurodevelopmental outcomes(11,19).

This trial expands upon earlier pilot studies by demonstrating the efficacy of MNAA within a larger, multicentre setting and across a diverse preterm population. Importantly, no adverse events were reported in any of the 100 infants receiving MNAA, affirming its safety profile (6). Furthermore, high clinician and parental satisfaction rates ($p = 0.278$ and $p = 0.565$, respectively) reinforce the intervention's clinical acceptability and feasibility for routine use in neonatal care units (6).

Nevertheless, the study is not without limitations. While randomization ensured baseline equivalence, blinding of intervention delivery was inherently limited by the visible placement of magnetic pellets on the auricle. This may have introduced observer bias, an issue similarly noted in previous neonatal acupuncture research (6,18). Moreover, although short-term benefits were evident, the study did not evaluate long-term neurodevelopmental outcomes. This represents a critical gap, as cumulative procedural stress during the neonatal period has been associated with alterations in thalamic development and disrupted functional brain connectivity later in life (11,19).

Despite these limitations, the findings of this trial position MNAA as a viable, safe, and effective non-pharmacological adjunct to current ROP examination protocols. The intervention aligns with broader efforts in neonatal care aimed at reducing opioid exposure while optimizing procedural comfort and minimizing stress-induced physiologic perturbations (6,19). Future research should focus on evaluating MNAA across repetitive procedural contexts and integrating objective biomarkers, such as heart rate variability, to quantify stress resilience and recovery more precisely (6,11).

In summary, MNAA significantly mitigated procedural pain and physiological stress responses during ROP examinations in preterm infants. The intervention holds substantial promise for improving neonatal procedural care, and its integration into standard pain management protocols may contribute to better short- and long-term outcomes in this highly vulnerable population.

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