Effects at 3 Months Corrected Age of a Parent-Administered Exercise Program in the Neonatal Intensive Care Unit: A Randomized Controlled Clinical Trial

Gunn Kristin Øberg, Gay L. Girolami, Suzann K. Campbell, Tordis Ustad, Ivar Heuch, Bjarne K. Jacobsen, Per Ivar Kaaresen, Vibeke Smith Aulie, and Lone Jørgensen

Øberg and Girolami are co- first authors

Corresponding author: Gunn Kristin Øberg: PT, PhD, Professor, Department of Health and Care Sciences, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway / Department of Clinical Therapeutic Services, University Hospital North Norway, Tromsø, Norway. E-mail: gunn.kristin.oeberg@uit.no

Gay L. Girolami: PT, PhD, Clinical Professor. Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, USA. E-mail: gayg@uic.edu

Suzann K. Campbell: PT, PhD, Professor Emerita, University of Illinois at Chicago, Chicago, USA. E-mail: skc@uic.edu

Tordis Ustad: PT, PhD, Department of Clinical Services, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. E-mail: tordis.ustad@gmail.com

Ivar Heuch: MSc, PhD, Professor, Department of Mathematics, University of Bergen, Norway. E-mail: ivar.heuch@uib.no

Bjarne K. Jacobsen: MSc, PhD, Professor, Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway / Centre for Sami Health Research, Department of Community Medicine, UiT - The Arctic University of Norway, Tromsø, Norway. E-mail: bjarne.koster.jacobsen@uit.no

Per Ivar Kaaresen: MD, PhD, Associate Professor, Pediatric and Adolescent Department, University Hospital North Norway, Tromsø, Norway / Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway. E-mail: per.ivar.kaaresen@unn.no

Vibeke Smith Aulie: PT, MSc, Section of physiotherapy, Oslo University Hospital, Ullevål, Oslo, Norway. E-mail:UXVIUL@ous-hf.no

Lone Jørgensen: PT, PhD, Professor, Department of Health and Care Sciences, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway / Department of Clinical Therapeutic Services, University Hospital North Norway, Tromsø, Norway. E-mail: lone.jorgensen@uit.no

Abstract

Background. Despite the risk of delayed motor development in infants born preterm, knowledge about interventions in the Neonatal Intensive Care Unit (NICU) and the effects of dosing is sparse.

Objective. To examine effectiveness of a parent-administered exercise program in the NICU on motor outcome at three months corrected age (CA) and the effect of dosing on motor performance.

Design. Randomized clinical trial.

Setting. University Hospitals in Tromsø, Trondheim and Oslo, Norway

Participants. 153 infants with gestational age $\leq$ 32 weeks at birth were randomly assigned to intervention or control groups.

Intervention. A 3-week parent-administered intervention designed to facilitate movements in preterm infants was performed in the NICU. Parents were asked to administer the intervention 10 minutes twice a day.

Measurements. Test of Infant Motor Performance (TIMP) was used to assess short-term outcome at three months CA.

Results. No significant difference in the TIMP z-score was found between intervention and control groups at follow-up three months CA, but a significant positive relationship was found between total intervention dose and TIMP z-scores. The adjusted odds of having a clinical z-score <0 at three months CA was about 6 times higher for infants with less than median intervention time than for infants with a longer intervention time.

Limitations. The number of infants born before 28 weeks was small. A spillover effect in favor of the control group was possible. We do not know if the infants received physical therapy after discharge from the hospital.

Conclusions. There was no difference in motor performance between the intervention group and the control group at three months CA. However, an increased intervention dose was positively associated with improved motor outcome.

Words manuscript: **4317**

Introduction

Despite increased survival rates for infants born preterm[1,2], adverse neurological outcomes are associated with low birthweight preterm infants.[1,3] The last trimester of pregnancy is associated with rapid brain development.[4] The **presence of preterm birth may contribute to a disruption** of genetically programmed patterns of brain development associated with factors such as gestational age at birth, clinical stability, acquired brain injury, bronchopulmonary dysplasia, and non-optimal environmental influences.[5-7] There is growing evidence that neuroplasticity facilitates structural and functional reorganization of the brain through experience and active participation,[8,9] implying that early intervention may alter neurodevelopment in infants born preterm.[6]

A number of early intervention programs aimed at improving outcomes for infants born preterm have been studied.[10-13] The most effective are those involving both the parent and the infant.[6,13,14] Many of these interventions have demonstrated significant and lasting effects on cognitive and behavioral outcomes in infants.[15,16] While the effects on motor outcomes are less robust,[13] interventions associated with improved motor outcomes specifically focused on motor skills.[13,14] These programs commonly involve both physical therapists (PTs) and parents[6] with the aim of moving the infant or **assisting the infant to move** into a variety of positions including facilitation of head and hands to midline.[14] Some studies have demonstrated intervention effects associated with positive motor outcome up to 24 months corrected age (CA),[13,14] but the duration and dosage of the activities vary.[6] Therefore, it remains unclear when to begin the interventions, and what dosages are most effective to improve motor skills.

The "Norwegian Physiotherapy Study in Preterm Infants" (NOPPI), a multicenter randomized

controlled clinical trial (RCT), evaluates whether a parent-administered intervention in the Neonatal Intensive Care Unit (NICU) improves motor outcomes of infants born preterm during the NICU stay and up to 24 months CA.[17] A 3-week individualized intervention program was designed to facilitate postural symmetry through balanced activation of ventral and dorsal postural muscles and incorporated activities as a basis for functional position changes. The authors previously reported improved motor outcomes on the Test of Infant Motor Performance (TIMP) from 34 to 37 weeks postmenstrual age (PMA), which favored the intervention group with an effect size of 0.4.[18] However, based on the General Movement Assessment, there was no difference between intervention and control groups in terms of fidgety movements[19] or movement quality at three months CA.[20] The present article reports on outcomes on the TIMP at three months CA and a post hoc analysis between intervention time and TIMP outcomes. Based on the positive findings **at 37 weeks PMA**, when the intervention ended, we hypothesized continued positive progress in overall motor development for infants in the intervention group compared with those in the control group. **The following** questions are addressed in this paper: 1) Does functional motor outcome at three months CA differ between groups? 2) Is there a relationship between the amount of intervention received and motor performance in the intervention group?

Methods

Design Overview

The study was a pragmatic**,** multicenter**,** single-blinded RCT assessing the effect of a preventive physical therapy program carried out in the NICU. In this study pragmatic implies that the RCT addresses the intervention as it occurs in routine clinical practice and not in an ideal setting. The study was conducted at three Norwegian hospitals (University Hospital of North Norway, Tromsø; St. Olav's University Hospital, Trondheim; and Oslo University

Hospital, Ullevål). Ethical approval was obtained from the Regional Ethics Committee (REC North: 2009/916-7). The data presented in this article comprise a part of the RCT. The analysis of the complete dataset is ongoing. The full study is registered at ClinicalTrials.gov NCT01089296.

Setting and Participants

Study population and sample size. Participants were recruited between March 2010 and October 2014. All infants born at gestational age (GA) ≤32 weeks, deemed medically stable at 34 weeks PMA, and whose parents understood and spoke Norwegian, were eligible. Triplets and higher pluralities, infants with malformations or syndromes, and infants having undergone major surgery were excluded. Parents were invited to participate in the study one week prior to the planned initiation of the intervention at PMA 34 weeks. The study was explained, and parents who agreed to participate signed an informed consent.

Sample size was calculated based on the primary outcome of the NOPPI, Peabody Developmental Motor Scales-II scores[21] at 24 months CA and **those results will be presented in a separate paper.** A difference of 0.5 SD between the groups was considered to be clinically significant. To ensure a statistical power of 80% was achieved to detect this or a larger difference at 0.05 (α) significance level, 63 infants in each group were required. We planned to recruit 150 infants to account for dropouts and the impact of including twins.

Randomization and Intervention

Randomization. A web-based system developed and administered by the Unit of Applied Clinical Research, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway, was used for randomization.

Stratification was based on GA at birth (<28 week and ≥28 weeks) and hospital. Twins were assigned to the same group because the intervention protocol made it impossible to withhold group assignment from the parents and the physical therapist who taught the intervention to the parents.

Intervention. The intervention has previously been described in detail[17] and was a modified version of Girolami's [22] handling and motor stimulation program for preterm infants. The intervention employed **guided** movement to improve postural control in prone, supine, side-lying and supported sitting. The primary aims were to improve head and trunk control and antigravity midline orientation of head, arms and legs in each position. The intervention in the positions mentioned above incorporated minute movements in all planes and intermittent adjusted compression over relevant muscle groups and joints. We added activities in which the infant was guided from supine to side-lying and from supine through side-lying to upright supported sitting. In the NOPPI study, the parent was trained by the PT to perform the intervention daily at the bedside. **Daily intervention was possible because the structure of the Norwegian maternity leave supports the opportunity for parents who come daily to the NICU to be with their infants.** The protocol also emphasized communication and social interaction between parent and infant.

The parent-administered intervention consisted of 15 different "play-exercises" that the PT could choose from based on each infant`s tolerance for movement and level of development demonstrated on the NOPPI baseline assessment. One or more activities in each position of the four positions were always represented. The PT met with the parents for three sessions to teach, revise and support parent learning. During session one, the PT explained and demonstrated the play-exercises for the parent. The PT taught the parents about physiological

and behavior responses observed in preterm infants and strategies to appropriately respond to these cues. Emphasis was placed on awareness of the infant`s cues before, during and after the play-exercises. The parent received a "Play-Book" that contained photos and written instructions for each of the exercises. During the second session, the parent performed the intervention under the supervision of the PT. **The PT observed the parent's performance of the exercises and provided input to enhance the delivery of each exercise in the protocol**. One week later, the PT scheduled a third consultation to answer questions and clarify delivery of the protocol. **Parents were invited to contact the PT if they were in need of additional support or clarification regarding the exercise protocol.**

Per the protocol, the parent was asked to administer the intervention up to 10 minutes, twice a day, for three consecutive weeks beginning at 34 weeks PMA and to **terminate the exercise protocol at 37 weeks PMA**. Parents were told that if the infant showed signs of stress, they could pause the intervention to calm the infant or terminate the session. A booklet containing boxes was provided for parents to record administration and duration of the intervention protocol twice daily. Parents were also asked to provide explanations when the intervention was not performed or if it was terminated. Regardless of adherence to the protocol, no actions were taken to alter compliance. Therefore, when fidelity was not being met, there were no actions taken.

All three NICUs applied principles from the Newborn Individualized Developmental Care and Assessment Program (NIDCAP)[23] as standard nursing care. If discharged from the hospital prior to 37 weeks PMA, the parents were asked to continue the intervention at home until their infant reached the termination age of the program. The infants in the control group

received no parental intervention, but parents were instructed in general information. Details of physical therapy provided after hospital discharge for either group are unknown.

Outcome Measures

The primary aim of this analysis was to evaluate the difference in motor outcome between the intervention group and the control group on the TIMP at three months CA. A secondary outcome was the strength of the association between the total intervention time received and motor outcome on the TIMP.

Procedure for baseline assessment at 34 weeks Post Menstrual Age

Test of Infant Motor Performance Screening Items

Prior to randomization, a baseline assessment of motor development was performed at 34 weeks PMA using the Test of Infant Motor Performance Screening Items (TIMPSI). The TIMPSI is a screening version of the TIMP (see below) and is valid for use from 34 weeks PMA until five months CA. To establish inter-rater reliability, the testing therapists attended a two-day training course on administration and scoring of the TIMP.[24] The therapists also met five times to discuss and reach consensus about the scoring based on videotaped TIMP assessments. **Moreover, r**aters completed the researcher reliability protocol developed by the TIMP publisher. All NOPPI testers achieved a reliability level of >.90.

The TIMPSI, composed of three subsets of items from the TIMP, takes approximately 20 minutes to administer. Depending on the infant`s score on the first set of 11 items, the examiner is directed to administer items identified as the “easy set” (ten items) or the “hard set” (eight items). Both the TIMP, and consequently the TIMPSI, address selective movements and postural control in supine, prone, supported sitting and standing, items which

aligned well with the main goals of the intervention. The TIMPSI test results were used to individualize the treatment protocol for each infant. At each hospital, the PT who administered the TIMPSI also taught the parent the intervention. Background factors at baseline were collected from interviews with the parents and from the medical records. Thus, the testing therapist was not blinded to knowledge of infant risk factors, baseline motor performance, or subsequent group assignment.

Procedure for outcome assessment at three Months Corrected Age

Test of Infant Motor Performance

At three months corrected age, a PT at each hospital blinded to baseline test scores and group assignment administered the TIMP. If the PT assigned to administer the post-intervention assessment inadvertently learned the group assignment but was the only person available, the test was video recorded and later scored by a PT unaware of group assignment.

The TIMP assesses postural control and selective movements and can be administered from 34 weeks PMA until five months CA, and standards for two-week windows were identified when the test was normed. The TIMP has 13 Observed Items and 29 Elicited Items and takes on average 30 minutes to administer. Studies have demonstrated that the TIMP is responsive to intervention in preterm infants.[18,25] TIMP raw scores were transformed into z-scores based on the normative performance of 990 U.S. infants.[26] In the present study this z-score is referred to as the "clinical z-score". A positive result indicates that the infant scores are above the mean of the normative group; a negative score indicates that the infant scores are below the mean.[26] It was intended that all post-testing be administered within the same two-week normative window; as close to the middle of the 12-13-week corrected age window as possible. Due to circumstances such as weather conditions and/or illness of the child or

parent, it was not always possible to perform the assessment during the preferred window. However, the infants' clinical z-scores were calculated for the appropriate CA at testing based on the normative table in the TIMP Manual.[27]

In a previous publication from the same trial,[18] the TIMP raw scores at 37 weeks PMA were calculated applying an alternative formula to calculate a statistical z-score, which results in a different mean and standard deviation. Using the infants' clinical z-scores does, however, give a more accurate measure of their functional motor development.

Statistical Analysis

A modified intention-to-treat analysis was performed; in case of missing values, the last measurement was carried forward for endpoint analysis. At baseline, differences between the intervention group and the control group were tested using chi-square-test or independent samples t-test. To examine whether the TIMP clinical z-score at 37 weeks PMA or at three months CA differed between groups, a linear mixed model was applied with adjustment for hospital as a fixed effect, taking into account the clustering effects of twin pairs by a random family effect.

The post hoc analyses were performed as follows: In the intervention group, the relationship between total intervention time in minutes logged by parents and the TIMP clinical z-scores at 37 weeks PMA and at three months CA was evaluated in a linear model. Total intervention time was represented by a regression term, with other terms describing the effects of potential confounders (hospital, sex, birth weight, and mother's education). Correlation between time used on the intervention and baseline measures that might be related to the infant's health:

gestational age, birth weight, number of days on ventilation, number of days on continuous positive airway pressure was examined using Spearman's rho (r_s).

Infants in the intervention group were further divided into two groups according to the median total time they received the intervention. For three children, the intervention time was by chance the median. Thus, there were not the same number of children in the two groups.

We estimated the odds ratios (OR) for having a clinical z-score below 0, vs. a z-score ≥0 if total time used on the intervention was < the median. Logistic regression analysis with adjustments for hospital, sex, birth weight, and mother's education was applied. Differences between groups that might be related to infant health were tested using a chi-square-test or independent samples t-test. Statistical analyses were performed with IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA).

Role of Funding Source

The Norwegian Fund for Postgraduate Training in Physiotherapy (grant number 1/370-00/09), Oslo, Norway funded this study. The funding source played no role in the design**,** conduct of the study or analysis and interpretation of the data.

Results

Figure 1 shows a flow chart of the 217 invited participants. Consent to participate was obtained for 153 (71%) children. After baseline assessment, 74 were randomized to the intervention group and 79 to the control group. Before start of the intervention period, 10 in the intervention group and three in the control group withdrew, leaving 64 and 76 in each group, respectively. Three of those who withdrew from the intervention group also withdrew

their consent for use of the baseline data. After the intervention was completed at 37 weeks PMA, but before the 3-months CA assessment, one participant in the control group withdrew and, for logistic reasons, one was not available for this assessment. Thus, 64 in the intervention group and 74 in the control group were assessed at three months CA, whereas baseline data was available for 71 children in the intervention group and 79 children in the control group.

Table 1 shows the characteristics of the infants at baseline. There were no significant differences between the intervention and the control group. With regard to twins, there were 5 pairs in the intervention group and 11 pairs in the control group. However, as shown in Table 1, the actual number of twins in each group is not consistent with the number of sets of twins because one infant died prior to recruitment and two infants were medically unstable and could not be recruited for the study. Fewer than 10% in the intervention and 15% in the control group had a diagnosis of intraventricular hemorrhage, periventricular leukomalacia, sepsis or bronchopulmonary dysplasia, and no significant group differences were found ($p \geq 0.34$). Moreover, the groups did not differ regarding number of days on ventilation, continuous positive airway pressure or oxygen ($p \geq 0.37$).

As shown in Figure 2, **when the baseline TIMPSI scores were recalculated using the clinical z-score calculation method, there was no significant difference between the intervention group and the control group** (estimated mean clinical z-scores = -0.32 (95% CI: -0.45 to -0.18) and -0.42 (95% CI: -0.54 to -0.30), respectively, p=0.43). However, at 37 weeks PMA the intervention group **had significantly** higher estimated **mean clinical z-scores than the control group on the TIMP** (0.03 (95% CI: -0.12 to 0.19) vs -0.24 (95% CI: -0.39 to -0.08), p=0.014). **At** three months CA**, with no intervention after 37 weeks PMA, there**

was no difference between the groups **on the TIMP** (estimated mean clinical z-scores = -0.04 (95% CI: -0.20 to 0.12) and -0.08 (95% CI: -0.23 to 0.06), p=0.57).

Among the 64 infants in the intervention group, parents of 59 (92%) maintained a record detailing the number and total time of each session. The mean as well as the median total time during the 3-week intervention period was 222 minutes or about half the recommended amount (420 minutes). Reasons for not performing the intervention or spending less than the intended time were consistently related to the infants' behavioral state (being sleepy, tired, hungry, or unwell).

Table 2 shows that there was no association between the intervention time and the TIMP clinical z-score at 37 weeks CA (p=0.42) after multiple adjustments. In contrast, there was a statistically significant positive relationship between intervention time and the TIMP clinical z-score at three months CA (p=0.003).

There was no significant correlation between intervention time and baseline measures related to the infants` health such as gestational age, birth weight, number of days on ventilation, number of days on continuous positive airway pressure, or number of days on oxygen ($p \geq 0.26$).

At three months CA, 28 infants had TIMP clinical z-scores <0. The adjusted odds of having a z-score below 0 was about 6 times higher for those whose parent had spent less than 222 minutes on the intervention as compared to those who reported more time (Table 3). The groups did not differ with regard to a diagnosis of intraventricular hemorrhage, periventricular leukomalacia, sepsis or bronchopulmonary dysplasia ($p \geq 0.24$).

Discussion

This study is the first pragmatic, randomized controlled clinical trial evaluating a parent-administered intervention performed before 37 weeks PMA. It **reconfirms** the results **of** the 37 week follow-up,[18] which showed that at 37 weeks the intervention group had significantly higher motor scores than the control group. At three months CA, this difference was no longer significant. **However**, **we did find that in the intervention group, motor function assessed at three months CA showed a significant positive relationship between increased intervention dosage and improved motor outcome at three months, confirmed in a separate analysis dichotomizing both variables.**

A recent systematic review,[14] evaluating motor development interventions for infants born preterm commencing during or post-hospitalization**,** found that motor interventions focusing on the infants' active movements in a variety of positions were the most beneficial for enhancing motor skills from birth to 24 months CA. While the effect diminished over time, at three months CA the motor-specific interventions showed a large and significant effect size for motor skills. Most of these interventions included developmental support for the infant and parenting support and education.[14] Although similarities exist in the activities and underlying theoretical framework in the previous and present intervention, our findings were not consistent with a beneficial outcome at three months. Among the reviewed motor interventions, however, the ones that continued beyond the neonatal period had the strongest effects on motor development in the longer-term.[14] Therefore one might propose that the NOPPI intervention performed for three weeks in the NICU, was not long enough to diminish motor consequences in the long-term.

However, an important finding in the present study is the significant linear relationship between increased intervention dosage and improved motor outcome at three months, confirmed in a separate analysis dichotomizing both variables. There is substantial reason to attribute the statistical relationship to increased intervention dosage, given recent research regarding the capacity of the CNS to structurally and functionally change in response to experience.[28,29] It is well known that experience-dependent neuro-plasticity can cause re-organization of the developing brain.[9,28,29] Experience-dependent re-organization accentuates improved adaptive function and learning over time.[4,28] Therefore, it is likely that the improved motor outcome in the infants who received greater amounts of intervention supports the concept that dosage matters. An alternative explanation could be that the infants who received more intervention time were healthier. However, we did not find intervention time was related to the infants' diagnosis or other baseline health measures. The fact that the significant association between intervention time and motor outcome was only observed at three months CA but not at 37 weeks PMA when intervention ended may reflect a more pronounced tendency for the intervention effect to last longer in infants with a larger intervention dosage.

A critical point to consider is that infants received only about half of the prescribed dosage of the intervention. Parents' reasons for spending less time on the intervention were solely related to the infants` behavioral state. In contrast, Girolami and Campbell[22] reported no such problems during treatment sessions for infants that had reached 34 weeks PMA, even though a comparable handling and motor stimulation program was administered twice daily for 12 to 15 minutes. However, in Girolami and Campbell's study, the PT administered the intervention. The parents in this study took notice of infant stress cues, but because the NOPPI lacks data on physiological variables (such as heart-rate) during intervention, it is difficult to conclude whether the shorter duration of intervention minutes truly indicates the

infants couldn't tolerate handling more than once a day. As parents frequently report lower self-confidence in caring for their tiny infant and increased care-giving burdens after giving birth prematurely,[6,14,30] we speculate that perhaps parents were unable to comply with the requested amount of intervention. Therefore, one may argue that monitoring of physiological variables during administration of the program and examination of parent well-being and stress would have strengthened the study providing an understanding of reasons preventing parents from doing the intervention as requested.

A recent survey[31] of parents compliance with home-exercise programs for children with developmental disabilities suggests that adherence depends on factors such as self-efficacy, perception of barriers and ability to perform the program. For parents in the NICU, the environment presents a context that is often perceived as challenging, strange and scary, perhaps affecting caregiving activities.[32] Support and guidance provided by the health care workers is considered of great importance to empower the parents.[32,33] Thus, for parents to see the importance of preferred frequency and duration of the intervention, they may have benefited from more training to adjust the intervention protocol based on infant response. This might have been accomplished by having the PT attend the intervention sessions during the first week to provide guidance for parental decision-making. Alternatively, another approach to achieve optimal dosing might be parents performing the intervention once a day and PTs administering the second intervention. Finally, continuing a home-exercise program after discharge has also been shown to be effective.[26]

A strength of this research is that it was a pragmatic randomized multicenter controlled clinical trial, with blinded outcome assessors and long-term follow-up. The solid randomization procedures undertaken resulted in homogeneous groups. Moreover, GA was

used as an inclusion criterion rather than birth weight, avoiding inclusion of more mature growth-restricted infants, which would have made the results difficult to generalize. In addition, no important changes were introduced in the three NICUs during the inclusion period, with the exception of NOPPI-intervention program.

There are several limitations that should be considered. In this study, the sample size was based upon power for the test to be administered at 24 months (PDMS) and not the TIMP. Another possible weakness is the limited number of extremely preterm infants, (born <28 weeks gestation (n=25)) available for recruitment during the study period. However, the extremely preterm infants enrolled were evenly distributed between the intervention and control groups diminishing bias related to group differences. Another weakness was a possible spillover effect in favor of the control group because of the lack of parent blinding. The potential spillover effect from the intervention group to the control group was reduced by instructing the parents in the intervention group not to disclose nor communicate the content of the intervention to other parents in their NICU. Finally, we do not know if the children received physical therapy after discharge from the hospital.

Lastly, we acknowledge that there was an issue with fidelity that relates to the therapy dose received and the motor outcome at three months CA. Because the average intervention dosage was only about half of that intended, we recommend that future research should address whether 1) infants born preterm are unable to tolerate the prescribed handling amount, 2) alterations in the parent education methods would increase compliance, or 3) a combined parent-and-therapist-administered intervention would improve the likelihood of obtaining the prescribed twice daily intervention dosage.

Conclusions

Although there was no significant difference on the TIMP between the two groups at three months CA, there was a statistically significant positive relationship between total intervention time and the TIMP clinical z-score. The odds of having a z-score below 0 was about six times higher for infants who had received less than 222 minutes intervention, indicating that a parent-administered individualized early motor intervention program in the NICU can produce a substantial effect on motor development in infants born preterm if the intervention dosage is at least as high as the median in our intervention group.

Acknowledgements

We extend our gratitude to the parents and their infants for their time and willingness to participate. The authors also gratefully acknowledge the University Hospital of North Norway HF, St. Olavs University Hospital Trondheim HF and Oslo University Hospital, Ullevål for their support through arrangements of personnel. Furthermore, we would like to express our gratitude to The Norwegian Fund for Post-Graduate Training in Physiotherapy for funding.

REFERENCES

1. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. *JAMA.* 2015;314:1039–1051.
2. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies. *BMJ Open.* 2012;345:e7976.
3. Stensvold HJ, Klingenberg C, Stoen R, et al. Neonatal morbidity and 1-year survival of extremely preterm infants. *Pediatrics.* 2017;139:1-9.
4. Brodal P. *Central Nervous System: Structure and Function (4th Edition).* USA: Oxford University Press; 2010.
5. Doyle LW, Anderson PJ, Battin M, et al. Long term follow up of high risk children: who, why and how? *BMC pediatrics.* 2014;14:279.
6. Spittle A, Treyvaud K. The role of early developmental intervention to influence neurobehavioral outcomes of children born preterm. *Seminars in Perinatology.* 2016;40:542-548.
7. Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. *Seminars in Perinatology.* 2016;40:497-509.
8. Merzenich MM, Van Vleet TM, Nahum M. Brain plasticity-based therapeutics. *Frontiers in Human Neuroscience.* 2014;8:1-16.
9. Mottahedin A, Ardalan M, Chumak T, Riebe I, Ek J, Mallard C. Effect of neuroinflammation on synaptic organization and function in the developing brain: Implications for neurodevelopmental and neurodegenerative disorders. *Frontiers in cellular neuroscience.* 2017;11:190.
10. Orton J, Anderson Peter J, Ferretti C, et al. Improving the outcome of infants born at <30 weeks' gestation - a randomized controlled trial of preventative care at home. *BMC pediatrics.* 2009;9:73.
11. Kaaresen PI, Rønning JA, Tunby J, Nordhov SM, Ulvund SE, Dahl LB. A randomized controlled trial of an early intervention program in low birth weight children: outcome at 2 years. *Early human development.* 2008;84:201-209.
12. Moore G, Lemyre B, Barrowman N, Daboval T, Moore G. Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: A meta-analysis. *Archives of Pediatrics & Adolescent Medicine.* 2013;167:967-974.
13. Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database of Systematic Reviews.* 2015:1-107.
14. Hughes A, Redsell SA, Glazebrook C. Motor development interventions for preterm infants: A systematic review and meta-analysis. *Pediatrics.* 2016;138:e20160147.
15. Landsem IP, Handegård BH, Ulvund SE, Tunby J, Kaaresen PI, Rønning JA. Does an early intervention influence behavioral development until age 9 in children born prematurely? *Child Development.* 2015;86:1063-1079.
16. Vanderveen J, Bassler D, Robertson C, Kirpalani H. Early interventions involving parents to improve neurodevelopmental outcomes of premature infants: a meta-analysis. *Journal of Perinatology.* 2009;29:343-351.

17. Øberg GK, Campbell SK, Girolami GL, Ustad T, Jørgensen L, Kaaresen P. Study protocol: an early intervention program to improve motor outcome in preterm infants: a randomized controlled trial and a qualitative study of physiotherapy performance and parental experiences. *BMC pediatrics.* 2012;12:15.
18. Ustad T, Evensen KAI, Campbell SK, et al. Early parent-administered physical therapy for preterm infants: A randomized controlled trial. *Pediatrics.* 2016:e20160271.
19. Einspieler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G, Hart HM. *Prechtl`s method on the qualitative assessment of general movements in preterm, term and young infants.* Cambridge: Cambridge University Press; 2004.
20. Fjørtoft T, Ustad T, Follestad T, Kaaresen PI, Øberg GK. Does a parent-administrated early motor intervention influence general movements and movement character at 3months of age in infants born preterm? *Early Human Development.* 2017;112:20-24.
21. Folio M, Fewell R. *Peabody Developmental Motor Scales, Examiner's Manual.* 2 ed. Austin, Texas: Pro-ed; 2000.
22. Girolami GL, Campbell SK. Efficacy of a neuro-developmental treatment program to improve motor control in infants born prematurely. *Pediatric Physical Therapy.* 1994;6:175-184.
23. Als H, Duffy FH, McAnulty G, et al. NIDCAP improves brain function and structure in preterm infants with severe intrauterine growth restriction. *Journal of Perinatology.* 2012;32:797-803.
24. IMPS l. Workshop in the test of infant motor performance. From research to practice. In. Tromsø, Norway: Girolami, GL; 2011.
25. Lekskulchai R, Cole J. Effect of a developmental program on motor performance in infants born preterm. *Australian Journal of Physiotherapy.* 2001;47:169-176.
26. Campbell SK, Levy KP, Zawacki KL, Liao KP-J. Population-based age standards for interpreting results on the test of motor infant performance. *Pediatric Physical Therapy.* 2006;18:119-125.
27. Campbell SK. The test of infant motor performance. Test user`s manual version 3.0 for the TIMP version 5. In. Chicago, IL 2012.
28. Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: windows of opportunity in the developing brain. *European Journal of Paediatric Neurology.* 2017;21:23-48.
29. Belsky J, de Haan M. Annual research review: Parenting and children's brain development: The end of the beginning. *Journal of Child Psychology and Psychiatry.* 2011;52:409-428.
30. Treyvaud K. Parent and family outcomes following very preterm or very low birth weight birth: A review. *Seminars in Fetal and Neonatal Medicine.* 2014;19:131-135.
31. Medina-Mirapeix F, Lillo-Navarro C, Montilla-Herrador J, Gacto-Sánchez M, Franco-Sierra M, Escolar-Reina P. Predictors of parents' adherence to home exercise programs for children with developmental disabilities, regarding both exercise frequency and duration: a survey design. *European journal of physical and rehabilitation medicine.* 2017;53:545-555.
32. Lutz KF, Anderson LS, Riesch SK, Pridham KA, Becker PT. Furthering the understanding of parent–child relationships: A nursing scholarship review series. part 2: Grasping the early parenting experience—the insider view. *Journal for Specialists in Pediatric Nursing.* 2009;14:262-283.

33. Nordhov SM. *A randomised clinical trial on the impact of early intervention on parental child-rearing attitudes and cognitive, motor and behavioral outcomes in preterm infants* [PhD]. Institute of Clinical Medicine University of Tromsø 2011.

TABLE 1. Baseline characteristics of the infants in the Intervention Group and the Control Group ("usual care").

	Intervention Group (n=71)	Control Group (n=79)	p-value
Gestational age <28 weeks, n (%)	10 (14)	15 (19)	0.42
Boys, n (%)	36 (51)	44 (56)	0.54
Twins, n (%)	12 (17)	23 (29)	0.08
Has no older siblings, n (%)	41 (58)	54 (68)	0.18
Birth weight, gram, mean (SD)	1417 (417)	1385 (368)	0.62
Social background factors			
Mother's age, years, mean (SD)	32.1 (5.5)	30.5 (4.9)	0.07
Mother's education, years, mean (SD)	15.6 (2.7)	14.9 (2.8)	0.15
Father's education, years, mean (SD)	14.5 (3.0)	14.6 (2.7)	0.83

Table 2. Relationship (β-coefficient) between total intervention time and motor performance (TIMP clinical z-score) 37 weeks postmenstrual age, PMA, and 3-months corrected age, CA (n=59)

	37 weeks PMA			3 months CA		
	ß	95% CI	p	ß	95% CI	p
*Total intervention time, hours	0.03	-0.06 to 0.11	0.50	0.14	0.06 to 0.22	0.001
†Total intervention time, hours	0.04	-0.05 to 0.12	0.42	0.14	0.05 to 0.22	0.003

TIMP; Test of Infant Motor Performance

CI, confidence interval

*Adjusted for hospital

†Additional adjustments for sex, birth weight, mother's education

TABLE 3. Odds ratio for a low TIMP clinical z-score by 3 month corrected age (z-score <0) according to intervention-time-categories

	Total		Odds ratio for a clinical z-score < 0			
	z-score < 0	z-score ≥ 0	OR*	95% CI	OR†	95% CI
Intervention time	n=28	n=31				
Low (< 222 min)	19	8	5.9	1.8 to 18.8	5.7	1.7 to 19.1
High (≥ 222 min)	9	23	1.0		1.0	

TIMP; Test of Infant Motor Performance

CI, confidence interval

*Adjusted for hospital

†Additional adjustment for sex, birth weight and mother's education

LEGENDS:

FIGURE 1. Flow of the participants through the study

FIGURE 2. Motor performance (estimated mean clinical z-score (95 % CI)) in the intervention group and the control group at baseline 34 weeks postmenstrual age, at follow up 37 weeks postmenstrual age (PMA) and at 3-months corrected age (CA) adjusted for clustering effects of twin pairs and hospital.

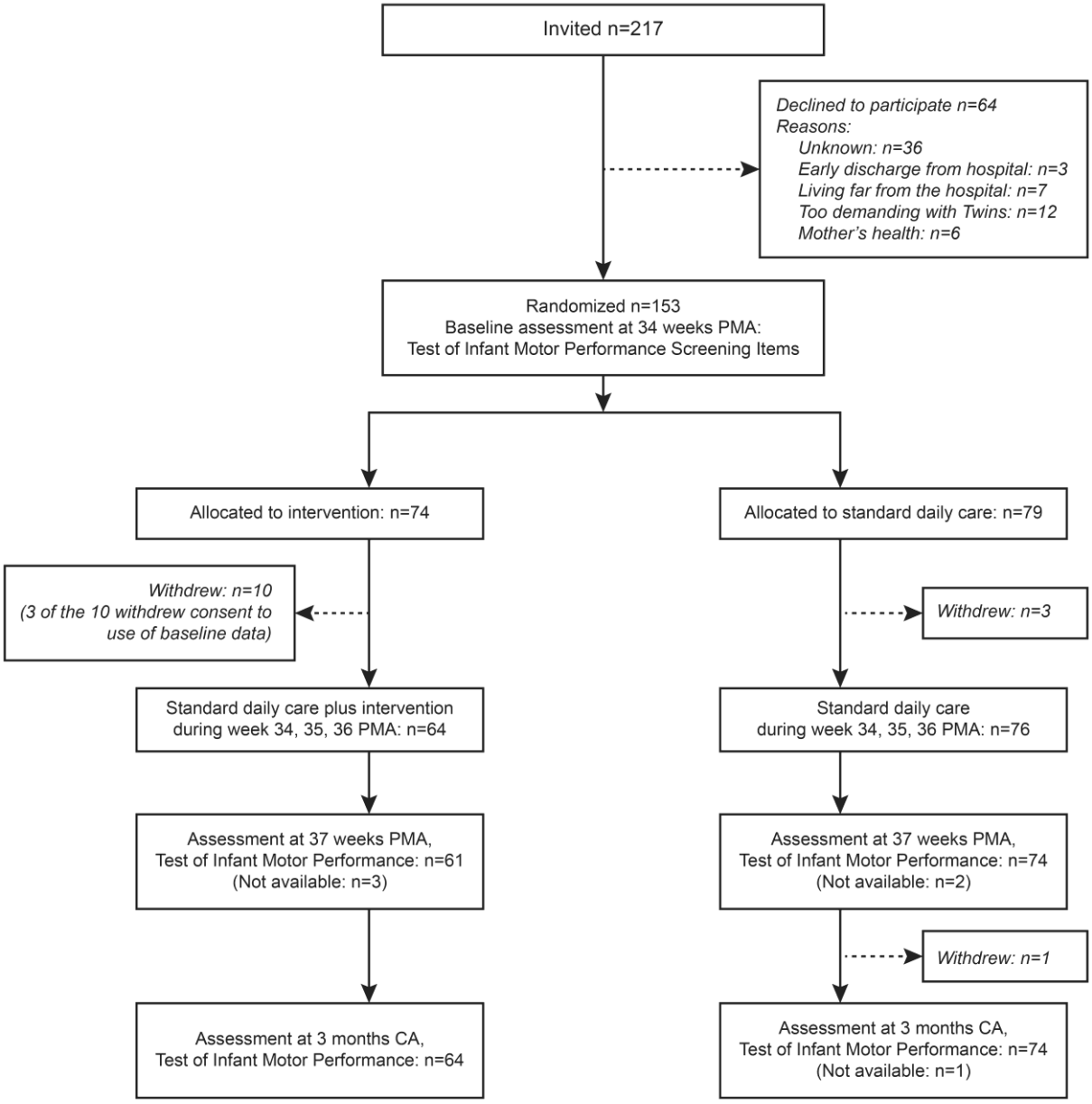

FIGURE 1. Flow of the participants through the study

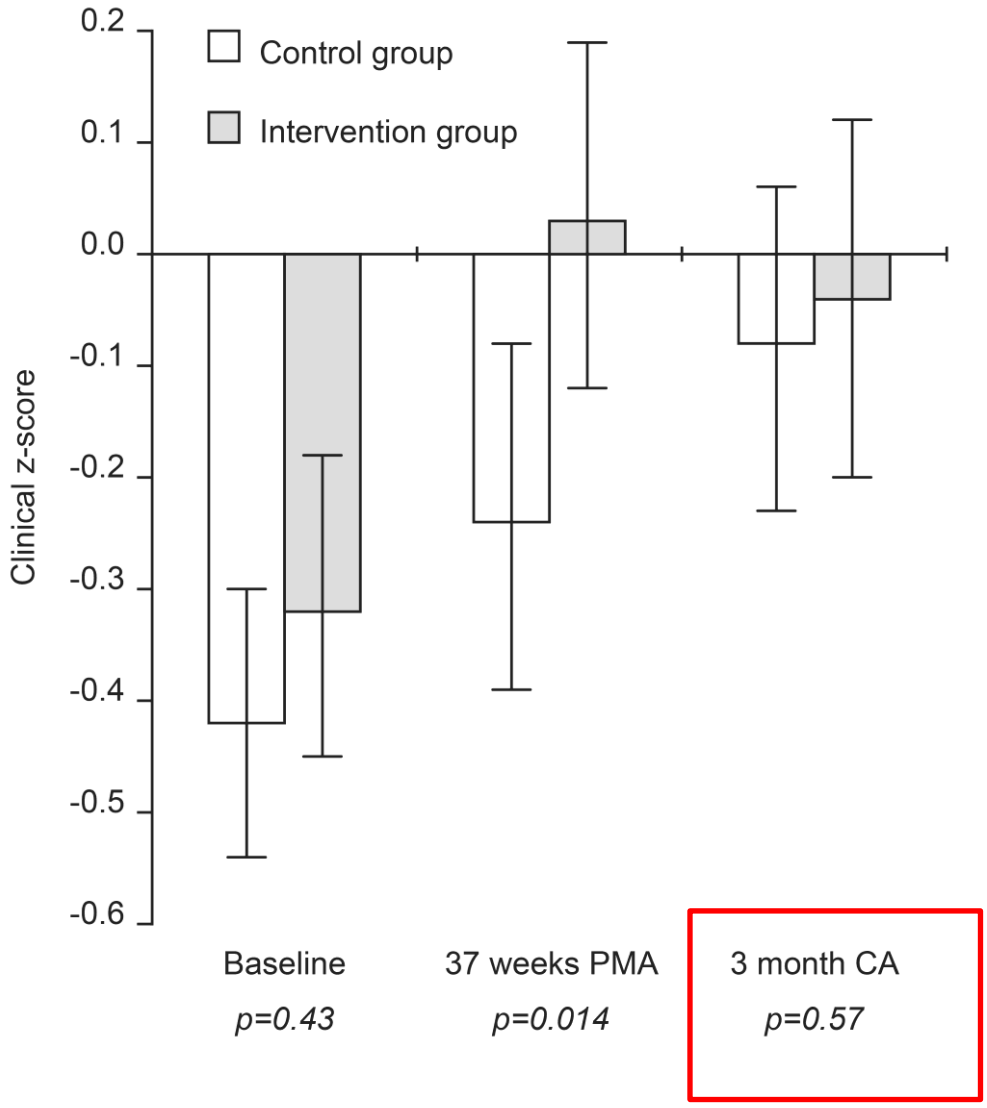

FIGURE 2. Motor performance (estimated mean clinical z-score (95 % CI)) in the intervention group and the control group at baseline 34 weeks postmenstrual age, at follow up 37 weeks postmenstrual age (PMA) and at 3-months corrected age (CA) adjusted for clustering effects of twin pairs and hospital.