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Do placebo effects associated with sham osteopathic procedure occur in newborns? Results of a randomized controlled trial

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KEYWORDS
Placebo;
Osteopathic manipulative treatment;
Placebo effect;
Sham

Summary
Background: Placebo effect has been largely studied and debated in medicine. Research focused mainly on children and adults but not on newborns. In osteopathy, few studies documented this effect and no research has been conducted in newborns.
Objectives: To assess the presence of placebo effect in newborns using sham osteopathic manipulative treatment.
Design: Randomized control trial.
Setting: Neonatal Intensive Care Unit in Italy.
Interventions: Two groups (103 patients each) of preterm infants aged 29—36 weeks without medical complications received routine pediatric care and osteopathic sham therapy was administrated to the study group only for the entire period of hospitalization.
Main outcome measures: Primary end point was the mean reduction of length of stay at discharge. Secondary objective was the change in daily weight gain.
Results: 206 newborns entered the study. No difference between sham and control group was found for the primary outcome length of stay (30.0 ± 20.3; 28.8 ± 18.9; $p = 0.70$). Multivariate analysis showed no difference between study and control group on length of stay. A negative association was found for gestational age (−2.33; 95% CI −3.81 to −0.85; $p = 0.002$), birth weight (−0.01; 95% CI −0.02 to −0.01; $p < 0.001$) and milk volume at study enrollment (−0.02; 95% CI −0.05 to −0.01; $p = 0.01$).
Conclusions: To the best of our knowledge, this study is the first in the field showing no placebo effect on newborns. Further discussions are opened concerning the age when placebo effect starts.

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Introduction

In the field of neonatology studies have demonstrated a statistical significant association between osteopathic manipulative treatment (OMT) and the reduction of length of stay (LOS) in a population of preterm infants.[1,2]

The accepted standards for clinical-trial design specify that the effects of an active treatment should ideally be compared to placebo's effects.[3,4]

According to placebo effect definition, that is benefit resulting from simulated treatment or the experience of receiving care, a wide variety of procedures can be considered placebo. In medical literature numerous studies used different placebos: pharmacological substances administered through any means, medical devices such as ultrasound,[5] sham surgery,[6,7] sham acupuncture and sham manipulation.[8]

Moreover, it is crucial to distinguish between pure and impure placebos.[9] Pure placebos are any inert substances or form of treatments, e.g. sugar pills. Impure placebos exhibit pharmacological or physical effects, but the effect has not been proven or is uncertain, e.g. antibiotics for viral respiratory infections. Considering ethical aspects, impure placebos seem to be more scientifically accepted than pure placebos.[10] As far as manual medicines are considered, scientific literature lacks of any formal discussion addressing the distinction between pure and impure placebos. Regarding mechanisms of action, substantial evidence is provided on the key role of prefrontal area on treatment expectation and recovery.[11] This seems to be associated with the activation of cognitive processes that, in turn, can elicit an objectively observable physiological response, the so-called placebo effect.[12]

Interestingly, a critical screening of the literature revealed that researches on placebo were mainly focused on the magnitude of the effect rather than on the age-onset.

Contradictory results turn up from RCTs, showing clinically significant placebo-associated improvements in as few as 5% or as many as 65%, depending on the particular study sample under investigation.[13] The majority of RCTs enrolled mostly adults[14] and rarely children[15] but, to the best of our knowledge, there are no studies reporting placebo effect in newborns. Moreover, no studies provided evidence about the age of placebo onset.

The rationale of the present study came from the need to assess whether or not preterm infants can effectively respond to placebo. Assuming that sham OMT is a kind of placebo impure treatment,[8] it is expected that sham OMT would reduce LOS in newborns. This could shed more light on the real effect of OMT and could suggest potential clinical and research implications.

Materials and methods

The primary objective of this single blinded randomized control trial was to assess the presence of placebo effect in newborns using sham OMT.

Outcome measures considered were: LOS at discharge and change in daily weight gain.

The sample enrolled was represented by preterm infants born and hospitalized in the neonatal intensive care unit (NICU) of the Pescara's civil hospital, from November 2010 to April 2011, free from medical complications with written informed consent from parents or legal guardians.

Exclusion criteria were: gestational age (GA) < 29 weeks, GA > 37 weeks, inclusion in to the study more than 14 days after birth, genetic disorders, congenital anomalies, cardiovascular abnormalities, neurological disorders, known or suspected necrotizing enterocolitis with or without gastrointestinal perforation, abdominal obstruction suspected or confirmed, patients with surgical issues, pneumoperitoneum and/or atelectasis, born to HIV positive mothers or drugs addicted.

All preterm infants included in the study were treated with standard medical care according to international and local unit guidelines.

In addition to routine care, subjects allocated to the study group received sham osteopathic care. In general osteopathic care is based on structural evaluation and treatment. The structural evaluation has the aim to locate somatic dysfunctions using standardized manual tests.[16] Diagnostic criteria for somatic dysfunction are focused on tissue alteration, asymmetry, range of motion and tenderness.[16] The osteopathic manipulative treatment is usually referred to a set of manual techniques aimed to relieve the somatic dysfunctions.[16]

In the present study, sham osteopathic procedure was based on standard structural evaluation, already used in previous studies[2] and executed with the infant lying down in the crib or incubator and focused on diagnosing somatic dysfunctions. Sham osteopathic treatment was based on the pre-determined protocol based on the application of light touch through the entire musculoskeletal system. In more detail, it consisted of light pressure applied for 2 min to the following infants' body areas: skull, chest, column, upper limbs, abdomen, pelvis and lower limbs. Newborns were maintained in supine position during the whole session. The total time for osteopathic evaluation and sham treatment was 20 min according to previous study setting.[2]

Conversely, patients from control group received only standard medical care by medical and paramedical staff.

To assure allocation concealment, 8 osteopathic practitioners were involved and randomly divided into two groups: sham and control practitioner. Each group was composed by 4 osteopaths and was respectively assigned to the study and control group. To provide blinding of outcome assessors and personnel, osteopaths from the two groups entered the NICU in different hours of the scheduled days. Sham practitioners provided sham treatment to the study group whilst control practitioners stood in front of all the incubators and/or beds for 20 min without touching newborns. Osteopathic service was provided twice a week, on Tuesdays and Fridays, for the entire period of newborns' hospitalization.

Patients were sequentially allocated to the study and control arms using a permuted-block randomization procedure (1:1 ratio) based on R software (version 2.12.3) as computer random sequence generator.[17]

An information technology consultant was in charge of randomization thirty minutes before the beginning of the osteopathic session. The randomization list was stored in a separated computer and the consultant was the only person to have access to it. Patients were assigned to the study and control group and were blinded to allocation. The medical