REVIEW

Oropharyngeal colostrum immunotherapy in premature newborns and neonatal mortality: a systematic review with meta-analysis

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Abstract

Objectives: to investigate the effect of oropharyngeal colostrum immunotherapy (OCI) on death incidence in preterm newborns.

Methods: this is a systematic review with meta-analysis, a study protocol registered in PROSPERO. The databases used were: Lilacs, Pubmed, Web of Science, Portal Capes, Scopus, REBEC and Clinical Trial; and, included studies published from 2007 to 2024, without language limitations. Randomized clinical trials that used OCI in premature infants and had death as an outcome, were selected. The review stages consisted of: protocol production, registration, study eligibility, data extraction, study quality assessment, data synthesis and meta-analysis. The software used was: Rayyan and Stata 10.0.

Results: 15 studies were included for qualitative and quantitative analysis. Regarding the assessment of global risk, the studies were considered to have a high risk of bias. In the quantitative analysis, the sample consisted of 1,497 premature infants; and, the meta-analytic measure showed a difference from the mean of RR=0.750 (95%CI=0.582-0.967), without evidence of heterogeneity between studies I2=0.0%; p=0.649 and positive trend in preventing the incidence of death in the intervention group compared to the control group.

Conclusion: the meta-analytic measurement suggests a possible positive effect of OCI in reducing neonatal mortality in premature infants.

Key words *Immunotherapy, Colostrum, Premature newborn, Perinatal death, Meta-analysis*

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Introduction

Prematurity is defined as birth before 37 completed weeks of gestation and is a sensitive marker on living and health conditions of a population that is considered a public health priority.[1] The World Health Organization has estimated that 152 million children were born prematurely in the last decade worldwide; and in 2020, around 1 million preterm newborns (PTNB) died from prematurity complications.[1] In 2020, 308,702 premature births were recorded in Brazil;[2] of these, 1,416 died of prematurity.[3]

Over the last few decades, various studies and strategies have been developed to understand and reduce the neonatal mortality rate in the world and in Brazil. One relevant measure is breastfeeding, as in addition to its nutritional characteristics, it contains immunobiological components that play an important role against morbidities and mortality.[4-7] Colostrum, in turn, stands out for its richness in immunomodulatory biofactors, which stimulate the cells of lymphoid tissues and can favor the maturation of the gastrointestinal tract and the immune system, an aspect that is especially relevant for PTNB, as they have immature immune systems and digestive tracts.[4]

The use of colostrum as immunological therapy - Oropharyngeal colostrum immunotherapy (OCI) - is a clinical practice using raw colostrum in small doses in the oropharynx of premature newborns, especially very low birth weight (VLBW) newborns, for immunological and non-nutritional purposes.[6] OCI is associated with a reduction in necrotizing enterocolitis,[8-11] ventilator-associated pneumonia,[11,12] late-onset sepsis,[10,11] feeding intolerance,[10] time to full enteral feeding,[7,10,11,13] length of hospital stay [9,11,14] and faster recovery of birth weight.[10,13]

Thus, OCI prevents unfavorable clinical outcomes that contribute to an increase in the mortality rate of PTNBs. However, there is controversy in the literature as to the positive effect of OCI on neonatal mortality.[9,10,15] The current study aimed to investigate the effect of OCI on the death incidence in PTNB, a relevant intervention that prevents health problems in premature infants.

Methods

This is a systematic review with meta-analysis of studies that evaluated the use of OCI in the death incidence in PTNBs, which followed the recommendations of PRISMA 2020[16] and the "Methodological guidelines: design of systematic review and meta-analysis of randomized clinical trials".[17]

A search was carried out in the following databases: Cochrane Library, VHL Cochrane Library, Center for Reviews and Dissemination (CRD), Clinical Queries, PubMed and International Prospective Register of Ongoing Systematic Reviews (PROSPERO), to check for registered protocols on the subject. The protocol for this study was self-authored and registered in the PROSPERO international database of systematic reviews, under the number CRD42022313945.

Inclusion and exclusion criteria of the studies

As eligibility criteria, human studies were considered, clinical trials being randomized, which used OCI in PTNB with gestational age less than 37 weeks, with the incidence of death as the outcome, without language limitation. Studies conducted in animal models and which dealt with colostrum intervention in aspects other than death were excluded. Studies published between 2007 and 2024 were selected in order to identify the first studies published on the subject under investigation.

Selection and eligibility of the studies

The databases used were: Lilacs, Pubmed, Web of Science, Portal Capes/MEC, Scopus, *Registro Brasileiro de Ensaios Clínicos* (REBEC) and Clinical Trial. The search strategy was constructed by the authors, with keywords, Boolean operators, filters and limiters used in the different electronic databases (Table 1). The selection of studies in journals indexed in the aforementioned databases was carried out until March 20, 2024, and included full texts and abstracts. In addition, during the search, other articles were identified in the list of references of published studies that had already been captured, which met the inclusion criteria and were possibly not captured by the strategies used.

The selection of studies was carried out by two reviewers independently (JRS and CCM), using the combination of descriptors that make up the PICO acronym for this study (P - Preterm newborn, I - OCI, C - Preterm newborn not treated with OCI (delimited by clinical trial) and O - Mortality among preterm infants) (Table 1); and with the help of the Rayyan application to eliminate duplicates and check for agreement between reviewers. The title and abstract were then read to select references and discard those that did not meet the eligibility criteria established for this review. Finally, the two reviewers read the selected articles in full.

For articles not available in the databases, contact was made with the authors; and if the title was suggestive of including the outcome researched, but the abstract was not available, the article remained in the application and moved on to the full text reading phase. If there was disagreement between the reviewers as to the eligibility of the article, a third reviewer (MSXR) was required for the final assessment.

Table 1

Search strategy with keywords and Boolean operators used in the different electronic databases, Feira de Santana, BA, Brazil, 2024.

Database	Strategies	N	Data
Lilacs	Infant, Premature [Words] and colostrum [Word] and Immunotherapy [Words]	2	03/20/2024
Pubmed	((“Infant, Premature”) AND (“colostrum”)) Filters: From 2014-2023, Humans,	132	03/20/2024
Web of Science	(ALL=(infant, premature)) AND ALL=(colostrum)) Filters: Document Types: Article Publication Date: 2005-01-01 to 2023-10-31 Advanced search done	135	03/20/2024
Portal Capes (Capes Portal) / MEC	Infant, Premature OR recém-nascido prematuro AND colostrum OR colostro AND clinical trial OR ensaio clínico. Filtros: Busca Avançada Tipo de material: todos os itens, Data de publicação: até 31/10/2023.	22	03/20/2024
Scopus	“infant, premature” AND “colostrum” AND “clinical trial” AND PUBYEAR > 2013 AND PUBYEAR < 2024 AND (LIMIT-TO (DOCTYPE , “ar”))	83	03/20/2024
REBEC (Registro Brasileiro de Ensaios Clínicos) (Brazilian Registry of Clinical Trials)	Colostrum	8	03/20/2024
Clinical trial	infant, premature | colostrum Condition: premature infant, Intervention: colostrum Study Status: All studies	17	03/20/2024

Data extraction and assessment of the quality of the study

Data was extracted and consolidated in a structured Excel table with the following information: type of publication, author, year of publication, title of article, objective, method of analysis, results, duration of follow-up, conclusions, journal, journal Qualis, year of research, research funding, type of funding, country of study, continent of study, statistical analysis of studies such as: crude RR, *p*-value, adjusted RR. Inclusion and exclusion criteria, sample size, mean age of participants, description of intervention and control, duration of OCI, confounding variables and study outcome.

The methodological quality of the selected studies was assessed using the Cochrane Collaboration's recommended risk-of-bias tool for randomized trials (RoB 2),[18] with regard to potential biases grouped into five domains (risk of bias arising from the randomization process, risk of bias in the blinding of participants and staff regarding allocation or adherence, incompleteness of data regarding outcomes, risk of bias in the evaluation of the outcome measure and risk of selective reporting of outcomes). An overall risk of bias was presented for each domain as: high (when at least one domain was judged to be at high risk of bias), some concern (when at least one domain raised some concern) and low (when all domains were at low risk).

Meta-analysis

All the published studies that met the inclusion criteria were included in the meta-analysis; and, as this is a new topic, there were few studies addressing the association investigated. Statistical heterogeneity was assessed using the i-squared (I^2) of the overall measure of association to identify the magnitude of the indicator and then the meta-analysis was carried out. The measures of association estimated were the relative risk and their respective 95% confidence intervals, obtained with fixed effect analysis using the Mantel-Haenszel method for binary variables using the STATA 16.0 statistical package. Sensitivity analysis was carried out using the risk of bias and the value of evidence and strength of recommendations were verified using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results

A total of 399 studies were retrieved from the databases, plus five studies identified by an active search of the study reference list. Fifteen of these were selected to make up the systematic review and meta-analysis, as can be seen in the study input-output flow diagram shown in Figure 1. The data extracted from the 15 studies in the systematic review is shown in Table 2.

Characteristics of the selected studies

The randomized clinical trial studies selected were published between 2007 and 2024 on the American (5), African (1) and Asian (9) continents. The intervention used was OCI, and the control groups used distilled water, exclusive parenteral fluids, routine care or standardized feeding regimens in the respective neonatal units. The routes of delivery of the intervention reported in the studies were: gastric lavage,[19] syringe drips[8,20-31] or oral hygiene with a swab.[32]

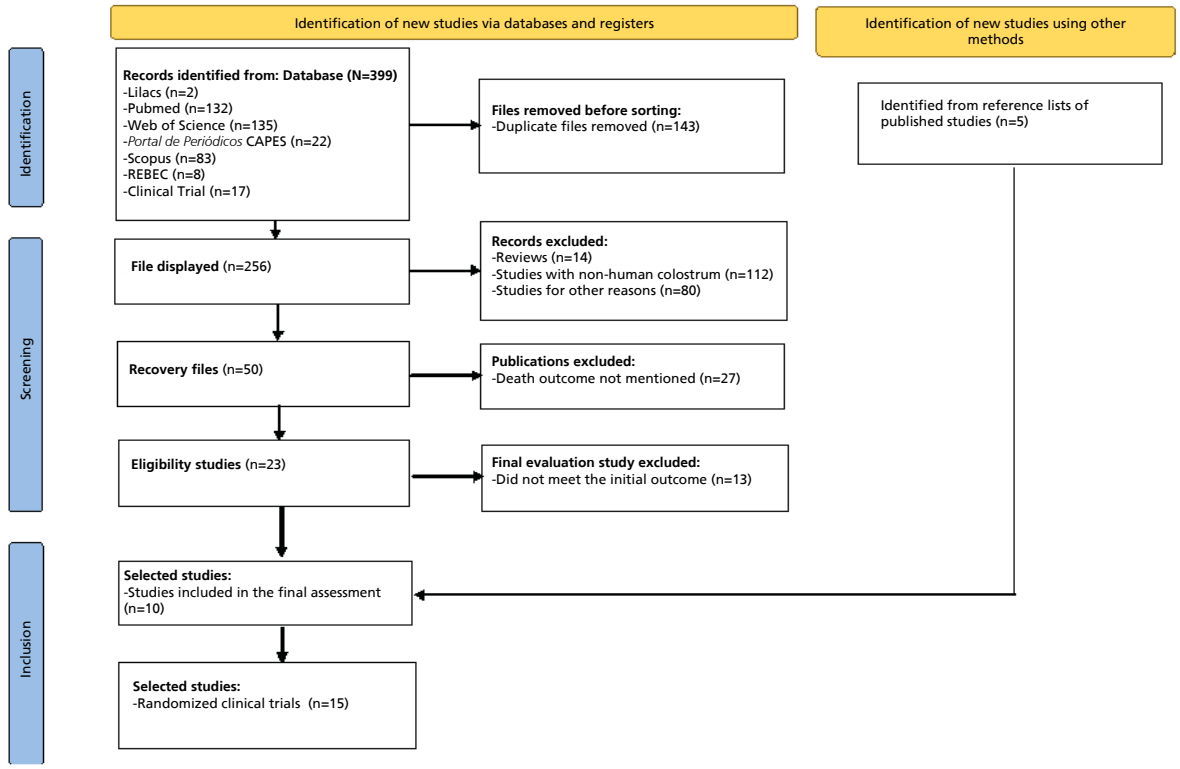
It should be noted that all the studies aimed to assess the efficacy of OCI on outcomes related to some health condition in newborns, with four presenting death as the primary outcome[23,29,31,32] and eleven as a secondary outcome.[8,19-22,24-28,30] None of the studies used found a statistically significant result for the investigation on the death outcome, and four of these studies did not report a *p*-value.[22,25,28,31] In addition, fourteen studies were published in the form of scientific articles in journals and one of the studies was an abstract presented at the European Society of Pediatric Gastroenterology, Hepatology and Nutrition congress.[31]

The risk of bias of the studies was assessed using Cochrane's RoB 2 tool (Figure 2) and showed that three studies were at low risk;[23,26,32] two were of some concern[24,25] and ten of the fifteen studies were at high risk of bias.[8,19-22,27,28,30]

The judgment of the risk of bias was assessed as an overall high risk of bias, due to the incompleteness of the outcome data (Domain 3) and the risk of bias in the assessment of the outcome measure (Domain 4) presented by the articles. Added to this factor is the diversity of OCI protocols between all the studies and the disparities in sample sizes. There was also insufficient description of the randomization, concealment and allocation of the samples, or even no description at all.[8,21,22,28,30,31] All the studies stated that the treatment was randomly allocated; however, five studies[21,22,25,28,31] did not specify the method used to generate the random sequence. Similarly, six studies did not mention allocation concealment methods;[8,19,25,27,29,31] of these, three reported that blinding of the intervention was not applicable due to the nature of the intervention;[8,25,29] and one study, despite presenting allocation concealment, did not mention blinding.[30] Among the studies, six were blinded to conduct the OCI.[20,22-24,26,32]

Figure 1

Flowchart for systematic reviews that included database and registry searches, according to PRISMA 2020.



REBEC=*Registro Brasileiro de Ensaios Clínicos; CAPES= Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.*

Probable methodological weaknesses were identified in most of the included studies, when assessed by RoB 2[22,25-30] (Figure 2). The quality of the studies included in this meta-analysis is presented graphically with percentages for each domain and the result of each RoB 2 assessment (Figure 2).

Meta-analysis

The meta-analysis showed a positive influence of OCI administration on reducing the incidence of death in PTNBs (Figure 3). The total sample size was 1,497 participants. The effect on the all-cause mortality rate between the groups was carried out with a total sample of 197 PTNB deaths between the intervention (83) and control (114) samples combined. All the studies showed deaths among the intervention and control samples, except for the studies by Sohn *et al.*[25] and Romero-Maldonado *et al.*[22] which showed no deaths in the treatment group; and no deaths in the control group were found in the articles by Rodriguez *et al.*[20] and Easo *et al.*[24]

The heterogeneity test between the studies showed an I^2=0.0%. The Q test showed p=0.649, which accepts the null hypothesis of homogeneity of the studies, so we can opt for a fixed-effect meta-analysis. The meta-analytical measure of the studies was RR= 0.750 (95%CI=0.582-0.967), showing that there was a protective effect of OCI on the incidence of death in PTNBs between the intervention and control groups. The analysis was dominated by three studies[27,29,30] which had a weight of 53.81%. The graph shows that there is an effect of the OCI intervention in preventing death in PTNBs.

A sensitivity analysis was carried out for the risk of bias, omitting three studies[20,22,24] which were at the extremes of the distribution of results (outliers) from the forest plot; and two of them 20,24 with less weight in the final analysis. The data remained unchanged, with homogeneity maintained (I^2=0.0%, p=0.835) and a meta-analytical measure of RR= 0.750 (95%CI=0.58-0.98), very similar to that of the final analysis.

The value of the evidence and the strength of the recommendations was verified using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and it was concluded that the ranking of the studies used in this meta-analysis, being clinical trials randomized, makes the evidence, a priori, classified as of moderate confidence. Thus, it is likely that additional research will have an important impact on our confidence in the estimate of the effect, and we believe that in the future it may change the estimate to high confidence in favor of the treatment.

Table 2

Characteristics of the fifteen randomized clinical trials that evaluated the effects of OCI administration on the outcome of death in premature infants, Feira de Santana, BA, Brazil, 2024.

Author, Year, Country	Objetive	Data Sample	Intervention and Control	Conclusions	Outcome/death
Patel and Shaikh,[19] 2007, India	To evaluate the effects of gastric lavage with breast milk in premature newborns compared to the use of exclusive parenteral feeding	Intervention group (n=40) Control group (n=40) Weight <1,750g GA <36 weeks	***Intervention:*** Gastric lavage every 3 h with 5 mL of their own mother's milk started within 4 hours of birth until the start of enteral diet with 3 ml/ Kg. ***Control:*** Use of exclusive parenteral fluids	The intervention reduced the number of days on parenteral fluids, risk of sepsis and length of hospital stay.	Intervention - 2 Control - 2 *p*=0.3 Not significant
Rodriguez *et al.*,[20] 2011, United States	To evaluate the effects of administering oropharyngeal colostrum to very low birth weight premature infants on their clinical outcomes.	Intervention group (n = 9) Control group (n = 6) Weight <1,000g GA <28 weeks	***Intervention:*** Use 0.2 mL of mother's own colostrum via oropharyngeal route every 2 hours for 48 consecutive hours. ***Control:*** Use of sterile water (placebo) via oropharynx every 2 hours for 48 consecutive hours.	Significant reduction in time to complete enteral feeding for PTNB treated with mother's own colostrum.	Intervention - 2 Control - 0 *p*=0,486 Not significant
Lee *et al.*,[26] 2015, Korea	To evaluate the immunological effects of oropharyngeal colostrum administration in very low birth weight premature infants.	Intervention group (n = 24) Control group (n = 24) Weight <1,003g GA <28 weeks	***Intervention:*** Use of 0.2 mL of colostrum via oropharyngeal route every 3 hours for 3 days, starting between 48 and 96 hours of life. ***Control:*** Use of sterilized water via the oropharynx every 3 hours for 3 days, starting between 48 and 96 hours of life.	The administration of oropharyngeal colostrum reduces clinical sepsis, inhibits the secretion of pro-inflammatory cytokines and increases circulating levels of immunoprotective factors.	Intervention – 3 Control – 6 *p*=0.46 Not significant
Sohn *et al.*,[25] 2016, United States	To evaluate the impact of oropharyngeal colostrum administration on the composition of the oral microbiota in PTNB.	Intervention Group - 6 Control Group - 6 Weight <1,500g GA ≤30 weeks.	***Intervention:*** Use of 0.2 mL of the mother's colostrum in the oral cavity (0.1 mL on each side of the cavity) every 2 hours for 46 hours, regardless of whether the RNPT-MBP was receiving trophic food. ***Control:*** Received routine care.	The oropharyngeal colostrum administration influenced the colonization of the oral cavity, with differences that persisted 48 hours after the end of the intervention.	Intervention – 0 Control – 1 *p*=not referred
Abd-Elgawad, *et al.*,[27] 2019, Eypgt	To evaluate the impact of administering oropharyngeal colostrum on reducing nosocomial sepsis.	Intervention group (n = 100) Control group (n = 100) Weight <1,500g GA < 32 weeks.	***Intervention:*** Use of 0.2 mL of maternal colostrum by dropper in the oropharyngeal pouch, tongue and cheeks every 2-4 hours, minutes before feeding by gavage. ***Control:*** Use of regular gavage with breast milk.	The intervention did not reduce sepsis, but had a beneficial effect on the early introduction of enteral feeding and on reducing the time to hospital discharge.	Intervention - 11 Control - 16 *p*=0.31 Not significant *Stratification for age 28 week: not significant.

Hariharan, *et al.*,[28] 2017, India	To evaluate the effects of oropharyngeal administration of colostrum on late-onset sepsis in LBWN.	Intervention group (n=56) Control group (N=56) Weight <1,250G GA < 32 weeks.	***Intervention:*** Use on the buccal mucosa of 0.2 mL of breast milk via syringe (0.1ml on each side of the mouth) every 6 hours, until 30 weeks corrected gestational age or the start of oral feeding. ***Control:*** Use of routine enteral feeding.	Oropharyngeal colostrum administration is feasible, safe and associated with a lower incidence of feeding intolerance and incidence of feeding intolerance and nosocomial sepsis in extreme prematurity.	Intervention – 2 Control – 2 *p*=not referred
Ferreira, *et al.*,[21] 2019, Brazil	To evaluate the effects of administering oropharyngeal colostrum on the incidence of clinical and proven late-onset sepsis and on immunoglobulin A (IgA) concentrations in very low birth weight newborns.	Intervention Group (n = 47) Control group (n = 66) Weight <1,500g GA < 34 weeks.	***Intervention:*** Use of 0.2 mL of maternal colostrum in the first 48 or 72 hours of life every 2 hours for 48 hours, 0.1 mL on the right oral mucosa and 0.1 mL on the left. ***Control:*** Use of 0.2 mL sterile water in the first 48 or 72 hours of life every 2 hours for 48 hours, 0.1 mL on the right oral mucosa and 0.1 mL on the left	This study could not confirm the hypothesis that oropharyngeal administration of maternal colostrum can reduce the incidence of late-onset sepsis and increase IgA levels.	Intervention – 2 Control – 8 *p*=not referred
Sharma, *et al.*,[8] 2020, India	To evaluate the effects of administering oropharyngeal colostrum to very low birth weight newborns in reducing necrotizing enterocolitis	Intervention Group (n = 59) Control group (n = 58) Weight ≤1,250g GA ≤30 weeks.	***Intervention:*** Use 0.2 mL of maternal colostrum on the oral mucosa, 0.1 mL on each side. Started after 24 hours of birth every 2 hours for 72 hours of life. ***Control:*** Received routine care.	Oropharyngeal colostrum administration is safe and reduces the length of hospital stay; however, it does not reduce the incidence of enterocolitis.	Intervention – 3 Control – 4 *p*=0.72 Not significant
Aggarwal *et al.*,[29] 2021, India	To evaluate the effects of administering oropharyngeal colostrum on reducing morbidity and mortality in premature newborns.	Intervention group (n=130) Control group (n=130) Weight: not identified GA <26-31 weeks.	***Intervention:*** Use of 0.2 mL of colostrum on the oral mucosa every 3 hours, starting after 24h of life and continued until oral feeding was started. ***Control:*** Use of 0.2 mL of sterile water on the oral mucosa every 3 hours, starting after 24 hours of life and continued until oral feeding was started.	Oropharyngeal colostrum administration of in neonates did not reduce the primary outcome of death, late-onset sepsis or necrotizing enterocolitis.	Intervention – 30 Control – 28 *p*=0.76 Not significant
Sudeep *et al.*,[30] 2022, India.	To evaluate the effects of administering oropharyngeal colostrum on clinical outcomes in premature infants between 26 and 30 weeks of gestation.	Intervention group (n=66) Control group (n=67) Weight: not identified GA: 26-30 weeks.	***Intervention:*** Use 0.2 mL of maternal colostrum on the oral mucosa, 0.1 mL on each side every 3 h., started at 24-72 h. of life, until 32 post-menstrual age and or start of oral feeding. ***Control:*** Use of 0.2 mL of distilled water on the oral mucosa, 0.1 mL on each side every 3 hours, started within 24-72 hours of life, up to 32 hours of post-menstrual age and/or the start of oral feeding.	The intervention reduced the incidence of late-onset sepsis and was considered a safe therapy.	Intervention – 10 Control –17 *p*=0.1 Not significant

Romero-Maldonado, *et al.*,[22] 2022, Mexico	To evaluate the effect of oropharyngeal administration of colostrum vs. placebo in the first 4 days of life in premature newborns ≤32 weeks of gestation on serum Immunoglobulin concentration, neonatal morbidity and total hospitalization days.	Intervention Group (n =46) Control Group (n =50) Weight: not identified GA <32 weeks.	***Intervention:*** Use of 0.3 mL of colostrum every 4hs, started from 24 postnatal for 4 days. ***Control:*** Use of 0.3 mL of distilled water every 4hs, started from 24 postnatal for 4 days.	The intervention increased serum IgA concentration on the 28th day of life, decreased the time to achieve full enteral feeding, birth weight recovery and length of hospital stay	Intervention – 0 Control – 6 *p*=0.06 Not significant
Jain *et al.*,[32] 2022, India	To evaluate the effect of oral hygiene with the mother's own breast milk on late-onset sepsis, mortality, days to obtain full enteral feeding, necrotizing enterocolitis, exclusive breastfeeding rates at discharge and total hospital days.	Intervention group = 55 Control group = 55 Weight <1,500g GA: not reported.	***Intervention:*** Use of 0.1 ml of mother's own milk through oral hygiene every 8 hours until oral feeding was achieved. ***Control:*** Received oral care without breast milk.	The intervention proved to be simple and safe, with a statistically significant reduction in late-onset sepsis and a non-significant reduction in mortality (secondary outcome) and an increase in exclusive breastfeeding rates at discharge.	Intervention – 5 Control – 9 *p*=0.252 Not significant
Rodriguez *et al.*,[23] 2023, United States	To evaluate the effect of oropharyngeal colostrum administration vs. placebo in reducing late-onset sepsis, necrotizing enterocolitis, death, length of hospital stay, time to complete enteral nutrition and complete oral feeding in premature infants	Intervention Group = 113 Control group = 107 Weight <1,250g GA: not reported.	***Intervention:*** Use of 0.2 mL of mother's own colostrum via the oropharynx every 2 hours for 48 consecutive hours, then every 3 hours until 32 weeks corrected gestational age. ***Control:*** Use of sterile water (placebo) via the oropharynx every 2 hours for 48 consecutive hours, then every 3 hours until 32 weeks of corrected gestational age.	The intervention did not reduce sepsis, necrotizing enterocolitis or death. There was a trend towards shorter hospital stays and better nutritional outcomes, but the results were not statistically significant.	Intervention – 4 Control – 3 *p*>0.05 Not significant
Mannan *et al.*,[31] 2023, Bangladesh	To evaluate the effect of oropharyngeal administration of colostrum on reducing the rates of necrotizing enterocolitis and mortality in premature infants	Intervention Group = 52 Control group = 40 Weight <1,800g GA: 34 weeks	***Intervention:*** Use 0.2 mL of mother's own colostrum via oropharyngeal route, after 24 to 48h postnatal, every 3 hours for 72 consecutive hours. ***Control:*** Received routine care	There was a positive effect on reducing the rate of necrotizing enterocolitis and the survival rate.	Intervention – 5 Control – 10 *p*=not referred
Easo *et al.*,[24] 2021, Kuwait	To evaluate the effect of oral therapy with colostrum or breast milk on clinical outcomes.	Intervention group = 24 Control Group = 24 Weight <1,500g GA: <33 weeks.	***Intervention:*** Use 0.2 mL of colostrum or breast milk by the oropharyngeal route, every 4 hours until oral feeding begins. ***Control:*** Use of 0.2 mL of saline solution by oropharyngeal route, every 4 hours until oral feeding begins.	Oral therapy with colostrum or breast milk reduces the time to hospital discharge.	Intervention – 2 Control – 0 *p*>0.05 Not significant

PTNB= preterm newborn; PTNB-PNB= very low birth weight preterm newborn; IgA= Immunoglobulin A; GA= gestational age; OCI= Oropharyngeal Colostrum Immunotherapy.

Figure 2

Assessment of the risk of bias and the methodological quality of the studies included in the review, Feira de Santana, BA, Brazil, 2024.

Study	D1	D2	D3	D4	D5	Global Risk
Sohn *et al.*,[25] 2016	+	!	+	+	+	!
Jain *et al.*,[32] 2022	+	+	+	+	+	+
Lee *et al.*,[26] 2015	+	+	+	+	+	+
Abd-Elgawad *et al.*,[27] 2019	+	+	-	-	+	-
Hariharan *et al.*,[28] 2017	!	+	-	-	!	-
Aggarwal *et al.*,[29] 2021	+	+	-	-	!	-
Sudeep *et al.*,[30] 2022	+	-	-	-	-	-
Mannan *et al.*,[31] 2023	-	+	+	+	+	-
Patel e Shaikh *et al.*,[19] 2007	+	+	-	-	+	-
Romero-Maldonado *et al.*,[22] 2022	+	+	-	+	+	-
Rodriguez *et al.*,[20] 2011	+	+	-	+	+	-
Ferreira *et al.*,[21] 2019	+	+	+	-	+	-
Sharma *et al.*,[8] 2020	+	-	-	!	+	-
Rodriguez *et al.*,[23] 2023	+	+	+	+	+	+
Easo *et al.*,[24] 2021	+	+	+	+	!	!

Risk of bias

+ Low Risk

! Some Concern

- High Risk

Domains

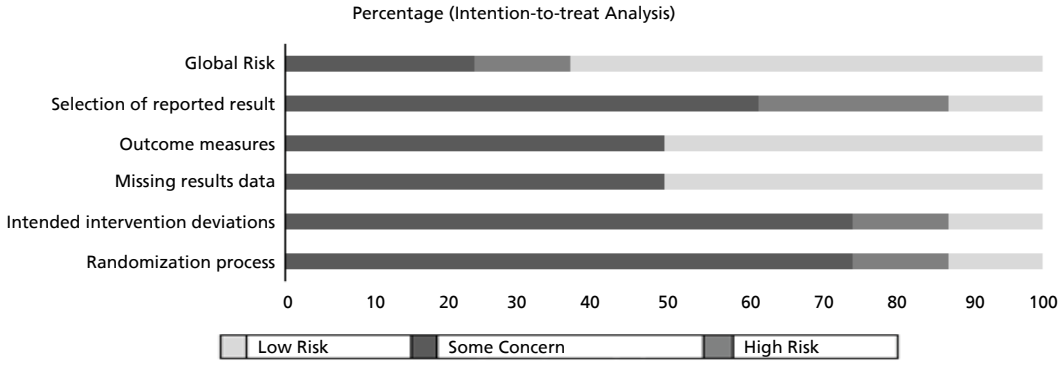
D1 Randomization process

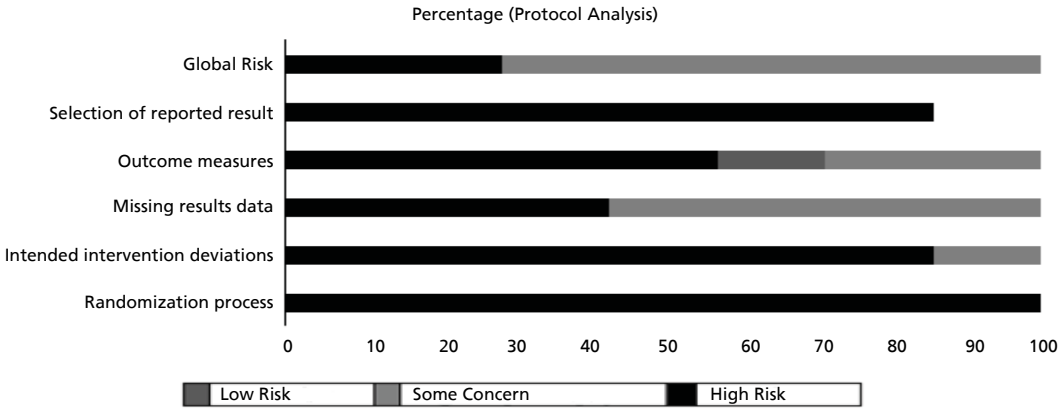
D2 Deviations from the intended intervention

D3 Missing outcome data

D4 Outcome measures

D5 Selection of reported outcome

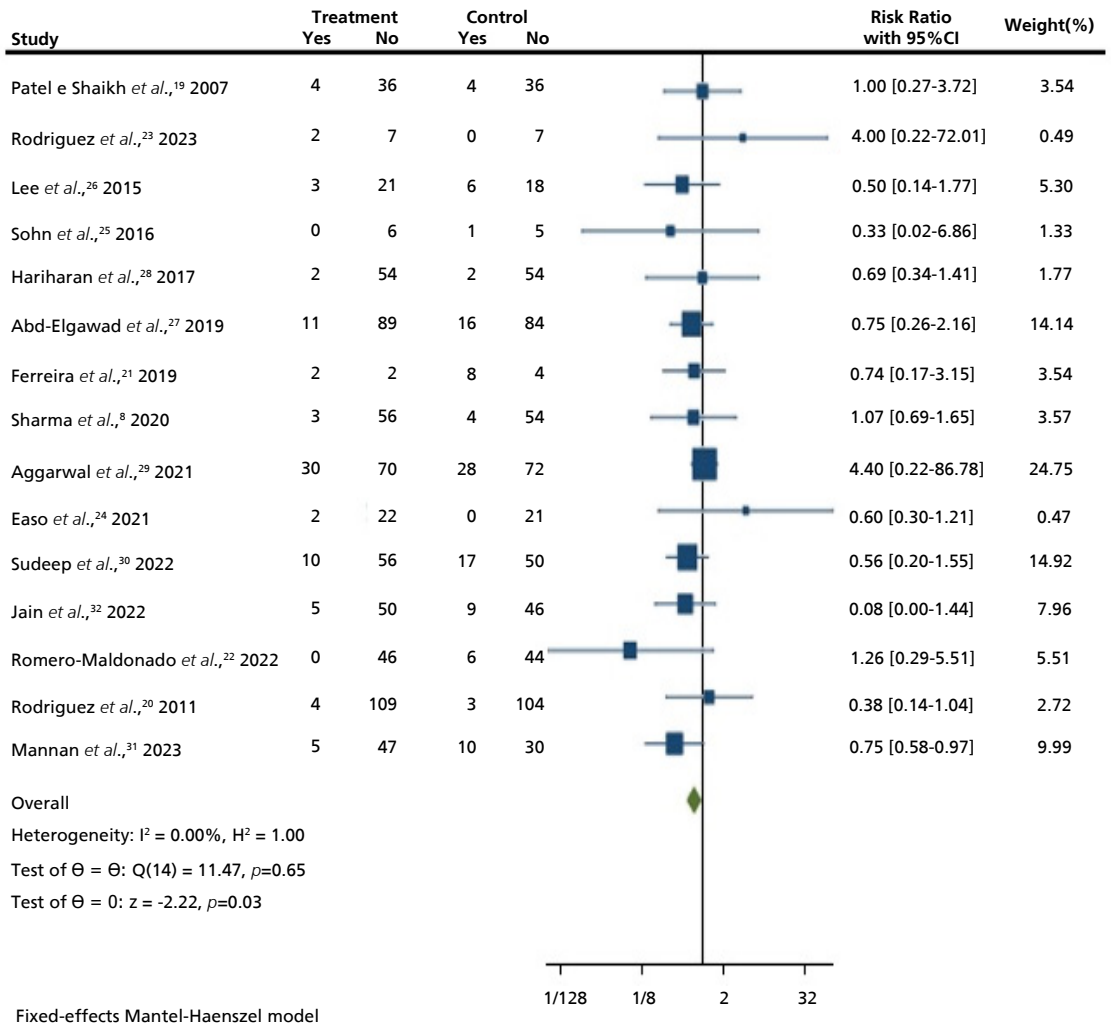




Source: RoB 2, 2023.

Figure 3

Meta-analysis of the OCI effects on death incidence in premature newborns, Feira de Santana, BA, Brazil, 2024.



OCI = Oropharyngeal Colostrum Immunotherapy.
Source: Stata 16.

Discussion

The current study, which included 1,497 PTNB, showed a trend towards a positive effect of OCI in reducing mortality in premature infants, by statistically synthesizing the numerical results of 15 randomized clinical trials, the primary studies that made up this meta-analysis.[8,19-32]

The findings of this meta-analysis are confirmed by the recent clinical trial conducted by Martins *et al.*[11] and two other meta-analyses recently published.[10,33] However, the meta-analyses by Huo *et al.*,[12] Peng *et al.*[9] and Slouha *et al.*[34] did not observe a reduction in the incidence of death in the treatment group compared to the control group.

It is worth noting that, among the studies evaluated, the positive effect of OCI on various events that contribute to health problems and neonatal death was demonstrated, such as: late onset sepsis,[19,22,26,28] feeding intolerance,[28] shorter time to obtain full enteral feeding,[20,27] a significant reduction in the time taken to use parenteral fluids,[19] shorter hospitalization time[8,19,20,27,32] and shorter time to recover birth weight.[20] Immunological benefits were also found, such as: higher IgA levels,[20,22] inhibition of inflammatory cytokine secretion,[26] increased circulating levels of immunoprotective factors[26] and establishment of beneficial oral microbiota,[25] when comparing the respective intervention groups, which used OCI, with the controls.

The findings of these studies reinforce the biological plausibility of OCI in reducing the incidence of neonatal

deaths, since it has been shown to have a protective effect against various clinical disorders that contribute to PTNBs deaths, especially those with very low birth weight. The World Health Organization stresses that, in order to reduce mortality in premature infants, it is necessary to prevent infectious diseases and ensure adequate nutrition, as these are important risk factors for this population,[1] whose vulnerabilities include immaturity of the immune system and digestive tract.[5,35]

The results also contribute to prior knowledge of the value and importance of colostrum in the first days of life. When a full-term newborn is breastfed directly, the lymphoid tissue in the oropharynx can absorb the immunoactive components of colostrum, thus favoring immune protection. For premature infants who cannot be fed orally, the immune protection of colostrum can be effectively provided by administering oropharyngeal colostrum.[5,35,36] PTNB who received oropharyngeal colostrum had lower levels of pro-inflammatory factors (IL-6, IL-8, TNF-α and IFN-γ) and higher levels of anti-inflammatory factors (IL-10), indicating that this route of administration plays an active role in the immune regulation of premature infants,[36] provided by the contact of protective biofactors present in colostrum with the lymphoid tissue of the oropharynx of premature infants.[5,35,36]

The results of the 15 studies that made up this meta-analysis also showed that OCI is a safe procedure for PTNBs.[8,19,21,28,30] Furthermore, as it is a simple, feasible and low-cost procedure, OCI can be used as a primary prevention measure, a strategy that can help to mitigate the risk factors inherent to prematurity, such as immaturity of the immune system,[20,22,25,26] immaturity of the digestive tract,[5,35] delay in starting enteral feeding[4,20,27] and length of hospital stay.[8,19,22,27,32]

We found a lack of standardization in terms of the technique used to manage OCI. Most of the studies (13) used an oropharyngeal colostrum administration protocol; however, the study by Patel and Shaikh[19] used gastric lavage with the mother's own milk, and the study by Jain *et al*.[32] administered colostrum through oral hygiene with a swab. The volume, frequency and duration of daily applications differed between the protocols, ranging from 0.1 to 0.3 mL; frequencies were every two, three, four, six or eight hours; and the minimum duration of the intervention was up to 48 hours and the maximum until enteral feeding began.

Of the fifteen studies, the intervention protocol of 0.2 mL every two hours for up to 48 hours predominated, and could be extended until the start of oral feeding in five studies.[21-23,25,27] In contrast, the data found by Fu *et al*.[10] suggests that the appropriate application of colostrum should be administered every four hours and the duration of treatment should be between eight and ten days. There is agreement between the studies on the benefits of early intervention.

A fundamental requirement in a meta-analysis is to ensure homogeneity in terms of clinical and methodological aspects between the individual studies that make up the data in the systematic review. We found that the test for heterogeneity between the studies included in the meta-analysis showed no heterogeneity, i.e. the individual studies evaluated showed homogeneity and consistency of results between them.

As for limitations, the main one is inherent to the methodology of meta-analysis, as it is based on published primary studies, which may have methodological restrictions. This limitation is in line with similar studies using the same methodology. On the other hand, what sets this study apart is that it specifically assessed the influence of OCI on the incidence of death among PTNBs, systematically followed research strategies using a protocol validated by PROSPERO, included 15 randomized clinical trials with homogeneity and consistency of results between them, making up a sample of 1,497 PTNBs; these measures can offset the limitations inherent in the studies on which it is based.

Conclusion

It can be concluded that the quantitative analysis of the 15 primary studies, comprising 1,497 PTNBs, included in the systematic review with meta-analysis, confirmed the assumption of the positive effect of OCI in reducing neonatal mortality in PTNBs. However, further primary research with higher statistical power is needed to prove this and other benefits related to OCI. The results of this study can provide a basis for the clinical implementation of OCI in neonatal units, as a way of preventing neonatal deaths, as well as supporting future studies. All of the above strengthen the use of OCI for PTNBs, which is a safe, simple and easy-to-implement measure.

Authors' contribution

Silva JR, Brandão HV, Ramos MSX, Costa MGR and Martins CC: conception, analysis and interpretation of the data, writing and revision of the manuscript. Vieira TO and Vieira GO: study design and critical revision of the manuscript. Silva JR is the researcher responsible for the study, working from conception to writing and revising the final version. All the authors have approved the final version of the article and declare no conflicts of interest.

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