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COLOSTRUM

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Introduction

Colostrum, also referred to as "liquid gold", is a biological fluid produced by the mammary gland.

It has a similar make-up to amniotic fluid that has been swallowed by the fetus throughout pregnancy. This gustatory similarity makes it an ideal fluid for transition to the life outside the womb. Colostrum is a vital food that is secreted shortly after birth and gradually changes in volume, consistency, components and appearance to transitional milk and mature milk. As the infant's gastrointestinal tract and the immune system develop, colostrum transitions over time to provide fewer immune factors and more calories and nutrients for growth.

Although colostrum changes over time, traces have been detected in breast milk for up to six weeks post-partum which may further reflect the infant-specific components required by the individual infant. Colostrum provides nutrition, enhances immunological protection and ensures growth. Colostrum also plays a role in tissue repair and development of lean muscle.

Colostrum contains at least 90 different biologically active substances such as immunoglobulins (IgG, IgA, IgM), lactoferrin, bifidus factor, growth factors, antioxidants and lysozymes which provide bactericidal and anti-inflammatory protection. These factors are essential for immune protection, maturation and development of gastrointestinal function and the development of the infant microbiome, which have implications on health and immunity.

While some immunological agents are transferred between the placenta and fetus, infants born prior to the third trimester do not receive the same passive IgG immunity as infants born at term. As a result, it is critical that these high-risk infants receive immunoglobulins from colostrum and breastmilk in order to provide some protection against pathogens. Without this protection, coupled with an immature gastrointestinal tract, co-morbidities that decrease gut perfusion, use of antibiotics that colonize the gut with pathogenic bacteria and delayed feeding , preterm infants are at higher risk compared to their term counterpart for necrotizing enterocolitis (NEC), late onset sepsis (LOS) or mortality. Several studies have used oropharyngeal colostrum (OPC) as an antimicrobial and anti-inflammatory modality to treat these morbidities. The exact mechanism of action, however, is unclear but likely multifactorial and initiated through absorption in the oral mucosa. This addition of Innovating Practice will explore a recent study that describes the importance of salivary secretory IgA levels, the most abundant immunoglobulin in colostrum, in very low birth weight infants. Glass and colleagues (2017) describes the effect of OPC on salivary sIgA levels in preterm infants and tested the hypothesis that these immunoglobulins play an integral role in prevention of neonatal infection.

The second study by Najman et al (2020) compared the concentration of transforming growth factor β (TGF-β) in colostrum in order to detect differences between preterm and term infants. The authors also wished to examine whether changes in TGF-β were observed in women who had a caesarian section birth compared to a vaginal birth. These findings may prove helpful in managing high risk infants in the Neonatal Intensive Care Unit (NICU).

The final study, a systematic review by Ma et al (2020), identified 8 studies that described how OPC can be used as a modality for preventing ventilator associated pneumonia (VAP) and other neonatal morbidities in very low birth weight infants. This publication provides direction for OPC use across the globe. The strength

of this publication was the ability to synthesize the results of many studies and have sufficient sample sizes to draw conclusive results.

Commentary following each review will identify next steps in OPC research and how clinical practice can be enhanced.

The overall theme in this edition is: Colostrum is species specific and changes over time to meet the immunological and nutritional needs of all infants; colostrum is readily available and inexpensive to use; colostrum plays a significant role in maintaining homeostasis at a time of vulnerability associated with prematurity or mode of delivery. Through ongoing analysis of this "liquid gold", full medicinal, pharmacological and immunological benefits can be achieved.

Key Points

- Infants born prematurely are at high risk for mortality and morbidity. The risk of acute illnesses is
  proportional to gestational age, reflecting the fragility and immaturity of their physiology
- Most pathogens causing late-onset sepsis come from the gut. It is hypothesized that NEC and sepsis likely involve a "dysbiosis" of the gut microbiota
- For preterm infants, enteral feeds are often delayed due to illness or acuity. Colostrum is their first feed. It is rich in immune factors, such as secretory immunoglobulin A (SIgA), lactoferrin, bifidus factor, and lysozyme. Their functions include: prebiotic activity, competition for pathogens and modulation of the immune system
- The concentrations of immune factors, particularly sIgA and TGF-β2, in human milk, are inversely proportional to gestational age
- The stability of these factors against enzymatic degradation, as evidenced by detection in the urine of infants who receive OPC, further supports the theory of absorption through the mucosal surface
- Colostrum is a readily available product that mothers are able to effectively produce. Health care professionals need to support mothers in their breastfeeding endeavors and describe the short and long term benefits of colostrum, transitional milk and mature milk
- Although the results vary, OPC has been shown to have an effect on NEC reduction, length of hospitalization, and other markers of breastmilk tolerance. Although it is a simple intervention, standardization of its use, administration techniques of the fluid and the amount of colostrum used is required for future comparative studies. However, until that time, and based on the low risk of the intervention, use of colostrum for early feeds is recommended.

Glass K, Greecher C, Doheny K. Oropharyngeal administration of colostrum increases salivary secretory IgA levels in very low birth weight infants. Am J Perinatol. 2017 Dec; 34(14): 1389-95

Background

Secretory IgA (sIgA) is the most abundant component in colostrum. Its function is to protect and maintain homeostatic regulation of intestinal, respiratory, and urogenital mucosal epithelia. sIgA functions to neutralize bacterial virulence factors, and downregulate proinflammatory responses normally associated with the bacteria, viruses and toxins. Concentration of IgA of colostrum is significantly reduced in transitional milk and mature milk. It is these properties that make colostrum a viable option for early feeds.

Data suggest that sIgA is an important component of colostrum that has immunological properties. However, much of the research has focused on the immune benefits provided by enteral breastmilk. Research has shown that small amounts of OPC is a safe and efficacious modality that could be offered when enteral feeds are not possible.

This pilot study sought to determine if early administration of colostrum, when enteral feeds were delayed due to immaturity, would increase salivary secretory IgA (SsIgA). They hypothesized that increased immunoglobulins in the colostrum would not only improve feeding tolerance but reduce length of hospitalization and decrease morbidities such as late onset infection or NEC. While the researchers recognized the immune benefits of enteral breastmilk, they were interested in an intervention that could be offered in advance of feeds; such as in the case of preterm infants in the neonatal intensive care unit.

30 preterm infants with birthweights less than 1500g were enrolled in the study. Infants were randomized to receive 0.2mls of OPC or sterile water every 3 hours for 7 days. The fluid was applied to the oral mucosa by using a cotton tipped applicator. Apnea and bradycardia during the administration of the fluid was monitored. Similarly, any adverse event during the study period was recorded

Enteral feeds with breastmilk or formula was not controlled and feeds were increased according to unit protocol. Total parenteral nutrition was continued until the infant achieved 100mL/kg/d. Saliva was collected on day 2 (enrollment), prior to colostrum or sterile water. Saliva was then collected on day 7 when the intervention was complete and again on day 14 by techniques used and validated in many previous studies. Mothers were supported to pump colostrum and breastfeeding was encouraged.

Results

A total of 30 infants were enrolled in the study with birth weights ranging from 520-1420g. SsIgA increased from baseline day 2 to day 7 in the group of infants who received OPC ($p < 0.00001$). However, SsIgA did not increase over time. Similarly, there were no differences in the time feeds were initiated, amount of breastmilk provided, tolerance of enteral feeds, time to full feeds or episodes of sepsis or NEC. There were no adverse events in either group of infants.

Conclusions

The authors found that administration of OPC was easily tolerated by very low birth weight infants. The intervention was safe and feasible and the ability to detect SsIgA was possible. The study did not see a difference in breastfeeding initiation or amount of breastmilk produced by participating mothers. They concluded that a larger study with infants of varying gestational ages would be required if treatment of NEC and infection was to be considered.

Commentary

Evidence from this study highlights the role of colostrum in immune protection by the presence of sIgA. The findings are consistent with other studies and suggest that infants who receive OPC have sIgA absorption that likely stimulates the immune system to achieve active immunity. These concentrations are inversely proportional to gestational age which may be a biological protective mechanism for the most vulnerable infants. It is interesting that this study did not find sIgA differences on day 14. Similarly they did not find differences in any of the clinical outcomes. While SsIgA had protective properties observed on day 7, the decline over time may have been related to sample size, which is what the authors concluded in this pilot trial focusing on the safety and feasibility of approach. It is possible that the lack of positive findings is purely by chance and that more study subjects would have changed the results. Larger studies with infants of varying gestational ages is worthy of further investigation.

Infants in this study began feeds quite late in their NICU stay (mean of 4 days). Only one infant in the study was tolerating full breastmilk feeds on day 7 of life. This may explain why differences were only detected on day 7 as the majority of their enteral intake was either OPC or sterile water. By day 14, most infants were receiving breastmilk feeds. Evidence has shown that sIgA levels in individual colostrum and breastmilk vary. Future studies should consider providing OPC immediately after birth so that any protective effect may be realized. Analysis of individual IgA levels may also increase our understanding of how/when immunological properties change over time.

An additional consideration is the parity of the mothers enrolled in the study. While there is conflicting evidence, previous pregnancies and breastfeeding as well as maternal nutritional status may affect IgA levels in colostrum. These variables would be an interesting addition to the body of evidence for IgA levels in preterm infant colostrum.

The next section will explore how transforming growth factor β (TGF-β) changes over time and how it regulates IgA production.

Najman B, Sibanda E, Radomska-Le´sniewska M. Does Caesarean Section or Preterm Delivery Influence TGF-β2 Concentrations in Human Colostrum? Nutrients 2020, 12, 1-11

Background

Preterm and acutely ill infants are at increased risk of NEC and other infectious and inflammatory morbidities. Colostrum has been shown to be best source of nutrition and immunological protection in the early days after birth. It is rich in immune mediators such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), insulin-like growth factor I and II, immunoglobulins and transforming growth factor β (TGF-β). The concentration of TGF-β changes during lactation with the highest level in the colostrum; again highlighting the species specific nature of the fluid. TGF-β regulates IgA production that works to protect against bacteria, virus and other pathogens.

There are some data to suggest TGF-β may also prevent early sensitization and atopic diseases as its function is to regulate lymphocytic response that may result in better gut tolerance, control of cell proliferation and control of wound healing. Although the results are inconclusive, TGF-β2 is thought to inhibit the inflammatory response and suppress the expression of macrophage cytokines, thereby reducing the risk of NEC in preterm neonates and acutely ill infants.

Studies have shown that surgery induces TGF-β1 synthesis and the authors hypothesized that mode of delivery may affect the concentration of TGF-β1 in colostrum. They wished to compare concentration of TGF-β2 in colostrum obtained from mothers who delivered vaginally or by caesarean section, and to compare the concentration of TGF-β2 in colostrum in mothers who have delivered term or preterm infants.

Two hundred ninety-nine mothers were included in the study with infants ranging from 25-41 weeks gestation. Colostrum was collected on the third day after delivery and concentrations of TGF-β2 were analyzed using a validated method used in previous studies.

Results

299 healthy women participated in the study. 192 (64.2%) had vaginal births and 107 (35.8%) delivered by caesarean section. 251 (84%) delivered a term infant > 37 weeks gestation and 48 (16%) delivered preterm infants.

The median concentration of the TGF-β2 cytokine in colostrum obtained by women who had term infants was 3899 ± 533 ng/mL compared to 4648 ± 772 ng/mL in women who had a preterm infant. Concentrations were inversely proportional to gestational age with the extremely immature infants <28 weeks gestation having higher concentrations of the TGF-β2 cytokines than those who were born > 28 weeks gestation. The concentration of the TGF-β2 cytokine in the colostrum obtained by women who delivered vaginally was 5240 ± 308 ng/mL compared to 7429 ± 730 ng/mL in women who had a caesarian section.

Conclusions

The authors concluded that colostrum containing high TGF-β2 after caesarean delivery and premature birth may prevent invasive gut pathology that can lead to NEC. They also indicated that further research on the utility of providing supplementary feedings fortified with TGF-β2 may prove fruitful.

Commentary

This study clearly shows differences in immune mediators, specifically TGF-β2, in colostrum based on gestational age. Preterm infants, compared to term infants, are at higher risk for a multitude of inflammatory or infectious diseases. These data support the hypotheses that colostrum is infant specific and biologically based on the individual needs. The authors further suggested that the higher levels in preterm colostrum suggests compensation for the immaturity of these functions in the neonate; higher immunological properties for those at highest risk for complications.

There are significant clinical implications for preterm infants. As it is not meant to be considered a "feed", colostrum should be offered as soon as possible after birth as protection against inflammatory morbidities. This requires ongoing communication with mothers.

Differences in the TGF-β2 levels in colostrum of women who delivered via caesarian section is more challenging to understand as many of the preterm infants were born via this method. The authors were not able to isolate the mode of delivery as a sole predictor of TGF-β2 levels and it was likely a combination of factors involved. What is important, however, is that infants born via caesarian section are at higher risk for morbidities such as transient tachypnea of the newborn, respiratory distress syndrome or pneumathoracies. Additionally, this mode of delivery is often required because the fetus is in distress. Whether there were underlying medical concerns with the fetus or the mode of delivery was a maternal choice, it is plausible that infants born via caesarian delivery would see increased benefits of early colostrum.

As a first study to examine how colostrum changes over time and by mode of delivery, these results suggest colostrum feedings are essential for smooth transition to extra uterine life. In the next section we will examine a meta-analysis examining the efficacy of OPC on a variety of clinical outcomes.

Ma A, Yang J, Zhang Z, Kang Y Oropharyngeal colostrum therapy reduces the incidence of ventilator-associated pneumonia in very low birth weight infants: a systematic review and meta-analysis. Pediatric Research. 2021 March 89(1): 54-62

Background

Premature infants are at high risk for Ventilator-associated pneumonia (VAP) due to their immunological immaturity and the presence of an endotracheal tube in their airway and need for mechanical ventilation for long periods of time. Bacterial pathogens invade lung tissue and significantly increase the risk of mortality, increases ventilator time, length of stay, and cost of care. Several studies have suggested that colostrum is an easy intervention that can be offered prior to feed initiation. Colostrum is thought to produce immune protection through stimulation of oropharyngeal receptors similar to what has been observed in critically ill adult patients who receive probiotics during mechanical ventilation. Probiotics are capable of reducing oral contamination and thereby the incidence of VAP, suggesting that the oropharyngeal mucosa can stimulate immune activation. These finding are the basis of using OPC for infants at risk for VAP.

Recent studies on OPC administration in preterm infants have demonstrated a marked immunological response. As a result, NICUs have begun to use OPC as a therapy for premature infants to further enhance immune protection. Results vary and a synthesis of information would help guide neonatal clinicians on optimal treatments for preterm infants.

A very recent literature search using keywords "oropharyngeal colostrum" or "colostrum" or "human milk" and "newborn" or "VLBW infant" or "low birth weight infant" or "premature infant" or "neonate" identified 204 studies examining the efficacy of colostrum for a variety of clinical outcomes (VAP, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), death, length of stay, time of full enteral feeding, proven sepsis, clinical sepsis, late-onset sepsis). Two reviewers assessed each of the studies using predetermined criteria for inclusion and analyzed the data in a combined/pooled fashion. Studies were included in the analysis if they included:

- Randomized controlled trials (RCTs) comparing OPC to placebo or no intervention
- Preterm infants < 32 weeks gestation
- Primary outcomes (e.g., VAP, NEC, ROP, proven sepsis, clinical sepsis, late-onset sepsis, and death) and secondary outcomes (e.g., length of stay and time of full enteral feeding).

Results

Eight RCTs were included in the analysis for a total of 682 infants (OPC group: 332; non-OPC group: 350). Infants randomized to OPC had significantly fewer incidences of VAP (P = 0.02) and achieved full enteral feeding earlier (P = 0.005). Infants who received OPC had a trend towards less NEC (P = 0.05), mortality (P = 0.09) and proven sepsis (P = 0.06). No differences were found in the length of NICU stay, BPD, ROP, or late-onset sepsis or death.

Conclusions

This meta-analysis, combining the results of many studies, found that OPC in preterm infants was a safe intervention that significantly reduced VAP and time to full feeds. Very promising results for NEC and sepsis were found but further research is required. Mothers were able to produce colostrum and breastmilk. Although there was no significant difference in breast milk intake between infants who received OPC and those who did not, the breast milk consumption was higher in the control/placebo groups, which may suggest that OPC can achieve improved clinical outcomes with less volume of ingested breastmilk.

Commentary

This recent meta-analysis combined results of 8 studies to provide powerful data to support the use of OPC in the management of VAP. While individual studies contribute to the body of knowledge, a meta-analysis combines similar studies to examine the overall effect. Only meta-analyses are able to achieve such high sample sizes.

The largest study included in the meta-analysis by Abd-Elgawad et al (2020) demonstrated that 0.2mls colostrum delivered via cotton applicator directly onto the oral mucosa significantly shortened the length of mechanical ventilation, which is the biggest risk factor for VAP next to low birth weight, prematurity, and parenteral nutrition. The authors posited that immunoglobulins in oral colostrum reduced the risk of VAP. This supposition is supported by 2 smaller studies (Lee et al (2015), Rodriguez et al (2011)) that found increased levels IgA, IgM, and lactoferrin in urine and saliva and an inhibition of the secretion of proinflammatory cytokines of infants who received OPC, suggesting that colostrum can increase neonatal immune factors and promote immunity.

Four of the studies showed decreased time to achieve enteral feeds in infants who received OPC. The pooled analyses highlight the importance of early colostrum in infants who cannot be fed. The potential immunotherapy for infants is significant. As colostrum provides functional nutrients and bioactive components that work to defend organisms against pathogens as well promote intestinal maturation and encourage colonization with healthy bacteria, early feeding practices can and should be adopted.

The incidence of NEC and sepsis was not statistically significant in the eight articles combined. However the trend is favourable and suggest other immunological factors are involved in the mechanisms of these inflammatory morbidities. Further analysis of the contributing factors such as structural and functional deficiencies related to epithelial barrier integrity is required.

The authors found that OPC was a safe and feasible intervention that garnered significant positive benefits.

They argue that the costs are low and the gains are high. Mothers were willing to participate in the studies and were able to produce sufficient amounts of both colostrum and breastmilk. It is important for neonatal care providers to continue to encourage mothers of preterm infants so that any and all benefits can be achieved.

This is the largest pooled analysis comparing OPC to placebo on incidence of VAP and other clinical outcomes. While the mechanisms of NEC and late onset sepsis remain unclear, data from this review can be used to change neonatal care. Knowledge of the benefits of colostrum observed in many countries around the world needs to be included in all communication with families.

Concluding Remarks

Human colostrum is species specific. Its components change over time based on the nutritional, physiological and immunological needs of infants. It has shown great promise as a nutritional supplement while awaiting enteral feeds in the NICU. It is well tolerated and easily digested. Colostrum has also been explored as a novel treatment for many inflammatory morbidities such as NEC or BPD.

Although there remains great mystery in the exact components of colostrum and what factors explain differences in its biologically active substances over time and between women, it is readily available, inexpensive and easily administered. Mothers who deliver a sick or preterm infant should be supported in their efforts to provide colostrum and breastmilk. It is an action that only they can perform and an action that continues to show promise as a neonatal treatment modality.

NICUs need to provide access to pumping supplies and private accommodations so that mothers can obtain sufficient colostrum for their infants. All infants will benefit from colostrum but for preterm and acutely ill infants, it should be the standard of care that is offered without question.

Additional References

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