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Role of Near-infrared Spectroscopy in the Diagnosis and Assessment of Necrotizing Enterocolitis

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Abstract

Near-infrared spectroscopy (NIRS) is a noninvasive, bedside diagnostic tool that could assist in the early diagnosis of necrotizing enterocolitis (NEC) in preterm neonates. NIRS is a safe and effective clinical tool in the neonatal intensive care unit to detect abnormal alterations in tissue perfusion and oxygenation. In addition, NIRS could also detect the complications of NEC, such as bowel necrosis and perforation. NEC is the most common gastrointestinal complication associated with preterm birth and critically ill infants. It is observed in 6–10% of preterm neonates, weighing below 1500 g, leading to considerable morbidity, mortality, and healthcare cost burden. The mortality rate ranges from 20 to 30%, highest in NEC infants undergoing surgery. NIRS is a promising diagnostic modality that could facilitate the early diagnosis of NEC and early detection of complications alone or with the imaging modalities.

Keywords

Near-infrared spectroscopy; Necrotizing enterocolitis; Neonatology; Newborn; Preterm infant

INTRODUCTION

Near-infrared spectroscopy (NIRS) is a clinical tool that provides a bedside method of noninvasively measuring continuous oxygen consumption and assessing for potential ischemia of tissues such as in the brain, kidneys, and intestinal tract. NIRS utilizes

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transparency of biological tissue to near-infrared radiation (700–1000 nm wavelength) to differentiate among various forms of chromophores, such as hemoglobin, myoglobin, and cytochromes.[1–5] In health care, it is used to detect tissue oxygenation levels, measure hemoglobin and myoglobin levels,[6,7] and assess hemoglobin oxygenation and tissue oxygenation noninvasively in real time.[1] One of its first medical applications was to monitor cerebral oxygenation and perfusion after traumatic brain injury and during cardiac and neurosurgical operations.[8] In pediatrics, it was first used to examine cerebral oxygenation in hospitalized preterm neonates.[9] The clinical application of NIRS in neonates has expanded in the last two decades, one of the domains being the early diagnosis of necrotizing enterocolitis (NEC).[8,10]

NEC is one of the most prevalent devastating diseases in neonates, affecting around 7% of preterm neonates with a birth weight below 1500 g in the United States and Canada.[11,12] The mortality rate is estimated to be around 20–30%, highest in those undergoing surgical intervention.[13,14] Bowel ischemia and eventual necrosis are pivotal aspects of the pathogenesis of NEC.[15] Plain abdominal radiography is the imaging modality of choice in NEC diagnosis; however, it often fails to detect the early stages of NEC.[16,17] Early detection of ischemic bowel may help in the earlier institution of necessary interventions and prevent bowel necrosis and perforation, thus reducing morbidity and mortality rates.[16]

In NEC, NIRS has been used to evaluate the effects of bowel perfusion deterioration on bowel ischemia and injury.[18] Besides the early diagnosis of NEC, NIRS can also differentiate between complicated and uncomplicated diseases in the first 48 hours after the onset of symptoms.[19,20] This review elaborates on the role and future implications of NIRS in the diagnosis and management of NEC.

TECHNICAL ASPECTES OF NIRS

The NIRS device contains a light-emitting diode (LED) that emits light rays of wavelengths 730 and 810 nm. These light photons pass through superficial and deep layers of tissue and are absorbed by oxygenated and deoxygenated hemoglobin differently.[21] The nonabsorbed fraction is reflected from the superficial to the proximal arc detector and the deep to the distal arc detector as illustrated in Figure 1. These signals are analyzed, and data from the superficial tissue are subtracted to estimate the tissue oxygen levels at a depth of 1–2 cm, called the regional saturation (rSO_2) of the underlying tissue.[22] The value of the rSO_2 reflects the tissue blood flow and tissue oxygenation. The device also calculates the amount of oxygen extracted from tissues called fractional tissue oxygen extraction (FTOE). FTOE helps to understand the balance between oxygen supply and demand of tissues.[8]

APPLICATION IN NEONATES TO STUDY SPLANCHNIC OXYGENATION

The application of NIRS in monitoring splanchnic tissue oxygenation in neonates has been validated by various studies.[23–26] Varela et al. demonstrated the correlation between superior mesenteric artery blood flow and gastric tissue oxygen saturation in an experimental animal model of hemorrhagic shock and abdominal compartment syndrome.[23] Dave et al. reported a rise in splanchnic tissue oxygenation after oral feeding in stable preterm

neonates.[26] Some of the studies mentioned above used cerebral oxygenation as a reference assuming that it is kept stable by cerebral autoregulation mechanisms during vascular insults to the gastrointestinal system. However, various studies have reported impaired cerebral autoregulation in clinically sick preterm neonates with variability in systemic blood pressure.[27–29]

Cortez et al., in a prospective cohort study, described the safe and effective use of NIRS to monitor splanchnic tissue oxygenation in the first 2 weeks of preterm neonates' life.[4] This study used arterial oxygen saturation by pulse oximetry as a reference instead of cerebral oxygenation index.[4] The splanchnic tissue oxygenation decreases over the first 9 days of life before increasing till day 14, and the fall in splanchnic rSO_2 leads to a rise in FTOE.[4,30] Mintzer et al. reported considerable variability in the splanchnic rSO_2 readings (~16%), which is higher than that in renal (6%), cerebral (3%), and pulse oximetry (1–2%) rSO_2 values.[31] The NIRS probe is usually applied in a paraumbilical position to avoid interference from the liver and bladder, as it has been demonstrated that supraumbilical and infraumbilical oxygen saturation correlate poorly with each other and cannot be interchanged for measuring splanchnic rSO_2.[32]

NIRS has been extensively studied in neonates to evaluate the significance of cerebral rSO_2 in hypoxic-ischemic encephalopathy, cerebral autoregulation, congenital heart disease, and postsurgical conditions.[8] There have been relatively fewer studies on the application of NIRS in the early diagnosis of NEC and the prediction of its clinical outcomes. However, various animal models and human neonatal studies have validated the reproducibility and feasibility of splanchnic oxygen saturation values and their association with bowel ischemia in NEC.[4,8]

ROLE IN NEC

Role of NIRS in Early Diagnosis and Predicting Outcomes

Patel et al. demonstrated the reduction in splanchnic rSO_2 in neonates with NEC compared to the normal and further reported that rSO_2 equal to or less than 56% was independently associated with around 14 times increased risk of NEC (odds ratio, 14.1; $p = 0.01$).[33] Therefore, the rSO_2 value may be interpreted as an early warning sign of NEC in vulnerable neonates. Due to the brain's higher metabolic activity, it extracts more oxygen from the blood, and consequently, the cerebral rSO_2 is less than the splanchnic rSO_2.[10] The cerebral rSO_2 is generally 5–15% lower than the splanchnic rSO_2.[30] The ratio of rSO_2 of cerebral and splanchnic tissue is called cerebro-splanchnic oxygenation ratio (CSOR). Fortune et al. reported a lower CSOR value in NEC and showed that the measurement of both rSO_2 and CSOR in neonates could predict acute abdomen with a 90% sensitivity and 96% specificity.[34] CSOR below 0.75 indicated a higher probability of the need for surgical intervention.[34] CSOR's reliability in NEC is reduced if concomitant cerebral conditions, such as intraventricular hemorrhage, are present.[4]

NIRS monitoring of preterm neonates with NEC within the first 8 hours of the onset of symptoms may predict complications and outcomes, such as bowel necrosis, perforation, surgical intervention, or death.[19] Schat et al. reported that significantly lower rSO_2 (cerebral

rSO_2 <72%, liver rSO_2 <60%) values within the first 8 hours after onset of symptoms predicted complications in NEC with a high sensitivity (100%) and a high specificity (80–100%).[19] A higher cerebral and splanchnic FTOE within the initial 24 hours of symptom-onset also predicted complications.[19] Loss of variability in splanchnic rSO_2 and high signal dropout may also predict the onset of NEC before clinical features become apparent.[4]

A case report on preterm twins by Zabaneh et al. also showed the association between reduced splanchnic rSO_2 values and complications in NEC.[35] Another case report corroborated the presence of splanchnic oxyhemoglobin desaturation in a preterm neonate with congenital heart disease who developed NEC.[36] A piglet model of NEC supported this link between low abdominal NIRS oxygenation values and future development of bowel ischemia and necrosis.[37] The possible reasons for this decline in splanchnic tissue oxygenation are bowel ischemia and necrosis, circulatory insufficiency in NEC compromise blood flow to less essential organs (including bowel), and bowel inflammation in early NEC.[19,38]

Role of NIRS in Transfusion-associated Necrotizing Enterocolitis

A temporal association has been identified between red blood cell transfusion (RBCT) and the development of NEC within 48 hours, which has been called transfusion-associated NEC (TANEC).[39,40] Cerebral and peripheral rSO_2 increases, and FTOE decreases after RBCT in preterm neonates.[41,42] Cerebral and splanchnic rSO_2 in neonates increased after RBCT in neonates with NEC (diagnosed before RBCT) and in neonates without NEC; however, splanchnic rSO_2 subsequently decreased in neonates who developed TANEC.[43] The current evidence in support of TANEC has a “very low” quality, primarily due to the lack of randomized controlled trials (RCTs) supporting the causal association in TANEC.[44,45] Lawrence et al. reported the lack of association between the rise in hematocrit values following RBCT and TANEC.[46] In very-low-birth-weight infants (birth weight below 1500 g), severe anemia (hemoglobin below 8 g/dL) instead of RBCT was associated with a heightened risk of developing NEC.[47]

The role of enteral feeding during and after RBCT transfusion in the development of TANEC is controversial. It has been hypothesized that enteral feeding during RBCT in preterm neonates may increase the risk of TANEC.[48] A prospective cohort study concluded that enteral feeding is possibly linked to bowel ischemia and TANEC.[49] An RCT conducted by Schindler et al. highlighted the lack of difference in splanchnic rSO_2 regardless of continuing or restricting enteral feeds during RBCT.[50] Further investigation into this phenomenon is warranted in larger RCTs.

Limitations of NIRS

Skin safety, especially in extremely premature neonates, was one of the significant concerns regarding the application of NIRS. Transcutaneous use of NIRS does not cause skin burns even if the probe is applied directly to the skin surface continuously for 48 hours.[32,51] Mepitel barrier on the NIRS sensor was used to rectify this issue.[30] The Mepitel barrier nullified the frequency of adverse skin effects, thereby facilitating the use of NIRS in the long-term monitoring of neonates in the intensive care unit.[30]

Most of the studies included in this review have not accounted for the variability in the splanchnic rSO_2 for changes in gestational age. Increasing gestational age is associated with the growing maturation of splanchnic vasculature and increasing metabolic activity in the gut.[30] The variability in the splanchnic rSO_2 readings was more than that in other tissues.[31] This might reflect uncertainty in the type of intestinal tissue sampled because the intestine is a multilayered, hollow organ with luminal contents and undergoing peristaltic movements. There is also confusion and lack of consensus about the best site over the abdominal wall to place the NIRS probe.[32] Supraumbilical probe placement might sample the liver, spleen, or stomach instead of the intestine; infraumbilical readings might reflect bladder and pelvic wall muscle tissue oxygenations in preterm neonates.[30]

There is also uncertainty about the influence of skin pigmentation and myoglobin over NIRS readings.[51] When assessing peripheral tissues with ample muscular mass, it becomes crucial to account for the contribution of myoglobin to the NIRS results. The heterogeneity in device probes and machine algorithms by various NIRS device manufacturers restricts extrapolating and comparing findings between devices.[8] This also limits the widespread use of the “normal” and “abnormal” values derived by various studies regarding the application of NIRS in NEC. Two observational studies had reported the inability of NIRS monitoring to differentiate between neonates with and without NEC when it was started shortly after the development of clinical features typical of NEC (bloody stools and abdominal distension).[34,52]

CONCLUSION

Our review highlights the potential use of NIRS in the continuous monitoring of splanchnic tissue oxygenation in preterm neonates to detect early pathogenic changes of NEC. NIRS is a safe and effective modality to incorporate in the neonatal intensive care unit to observe tissue perfusion and oxygenation alterations. It can also differentiate between complicated and uncomplicated NEC, thereby helping us in individualizing the management. Moreover, it might also help to decide feeding protocols in neonates recovering from NEC.

However, there are various limitations to its widespread clinical use. A couple of studies have concluded that NIRS could not diagnose NEC after the onset of clinical features.[34,52] NIRS can alert and warn neonatologists about the beginning of bowel ischemia; however, it might not differentiate between NEC and other intestinal ischemic conditions during the early phase of disease satisfactorily.

There is a lack of consensus among device manufacturers and coordination between researchers worldwide to create a reproducible dataset consisting of “normal” readings for the various tissue oxygenation parameters. Large-scale longitudinal studies are needed to produce such a clinically valuable dataset and standardize the use of NIRS in the diagnosis of NEC.

Recent advancements in NIRS have widened the electromagnetic spectrum of the sensors to create a novel method called broadband optical spectroscopy (BOS).[53] Further research

in human neonatal models studying the implementation of NIRS and BOS in the early detection of NEC is required.

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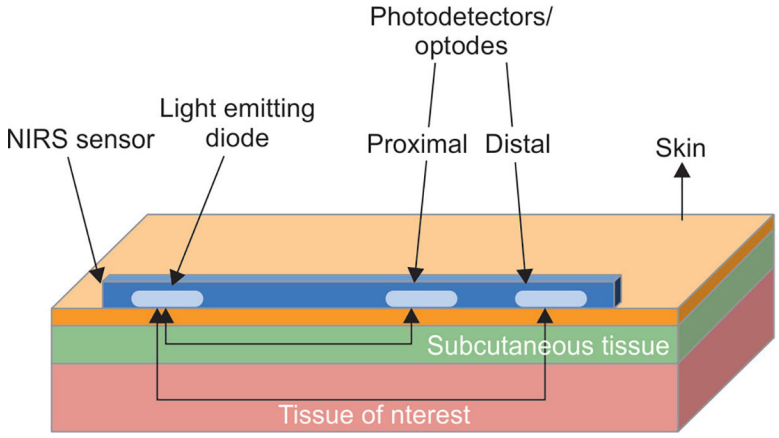

Fig. 1:
Technical aspects of NIRS