

EFFECT OF MINIMAL ENTERAL NUTRITION ON SUPERIOR MESENTERIC ARTERY (SMA) BLOOD FLOW VELOCITY IN PREMATURE INFANT

By

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ABSTRACT

Background: Minimal Enteral Nutrition (MEN) is reported to improve gastrointestinal disaccharides activity, hormone release, motility, and microbial flora. Clinical benefits include improved milk tolerance, greater postnatal growth, reduced systemic sepsis and shorter hospital stay. Very little is known about its effect on Superior Mesenteric Artery (SMA) blood flow velocity in premature infants.

Aim: the aim of this study is to detect changes in superior mesenteric artery blood flow occurring in preterm infant after MEN.

Patient and Method: It is a pretest-posttest prospective cohort study. SMA blood flow parameters were measured with Doppler Ultrasonography on SMA for analysis of Doppler flow velocity waveforms, that includes end-diastolic velocity, peak-systolic velocity, time-averaged mean velocity, resistive index and pulsatility index on 40 stable preterm neonates (gestational age range 28-33 weeks, weight at examination range 1000-2800 g, postnatal age range 1-4 days). They were admitted to the neonatal intensive care unit of Al-Zahra University Hospital during the period from July 2016 to December 2017. Measurements were performed before and after minimal enteral feeding. The baseline SMA blood flow was measured before test feed (10 to 15 ml/kg/day) and repeated 30 minutes after the feed.

Results: Comparing SMA velocities and indices before and after minimal enteral nutrition indicated a significant increase in peak systolic velocity (PSV), end diastolic velocity (EDV) and time- average mean velocity (TAMV), and a significant decrease in pulsatility index (PI) and resistance index (RI) after 30 min from MEN. the mean flow velocities of the (SGA) group were significantly higher than (AGA) group. the mean flow velocities of the early fed group were significantly higher than late fed group No correlation has been found between SMA parameters and studied vital signs or SpO₂.

Conclusion: MEN improves SMA blood flow especially in small for gestational age, thus it might influence the structure and promote development of the premature infant's gastrointestinal tract.

Recommendation: use of early minimal enteral nutrition especially in very premature baby and should be used as an adjunct to parenteral nutrition.

Keywords: Duplex ultrasound, preterm, minimal enteral feeding, SMA.

INTRODUCTION

Immediate survival, and subsequent growth and development of preterm infants depends largely on ensuring adequate nutrition. Due to concerns associated with rapid enteral feeding, such as the increased risk of necrotizing enterocolitis (NEC), total parenteral nutrition (TPN) has been widely used to deliver adequate calories to sick neonates in their initial few days. However, prolonged TPN is associated with complications and concerns. Therefore, the concept of minimal enteral nutrition (MEN) was evolved (Agarwal et al., 2001). It is also known with other names including gut priming, trophic feeding, and early hypocaloric feeding. This practice is introduced in the late 1980s to overcome the lack of gastrointestinal (GI) stimulation during TPN, while minimizing stress to the sick infant (McClure 2000). In this practice, preterm infant is fed by minute volumes of enteral feeds (volumes ranging from 0.1 to 24 ml/kg/day have been used with a typical value ranged from 0.5 to 1 ml/kg/day), to stimulate

the developing GI system and supply nutrients to it. Currently there is no evidence of any adverse effects following trophic feeding practice. Very small, sub-nutritional, quantities of enteral food had a potent effect on the release of enteroglucagon, a probable trophic hormone for the gut. It is usually used at the same time with TPN (Schanler, 2005).

Little is known about effect of MEN on the superior mesenteric artery (SMA) blood flow in premature infants. The splanchnic circulation accounts for 20% of cardiac output, and even it may contain one-third of the blood volume at sometimes (**Jacobson, 1991; and Mathias, 1997**). SMA is a large - caliber vessel that supplies the small intestine and the ascending colon. As the intestinal blood flow depends on this single vessel, changes in SMA blood flow patterns can have significant physiologic effects on the bowel (**Carver et al., 2002**).

Duplex ultrasound (DU) is a valuable tool for the assessment of blood flow in many vascular territories. Its application to the superior mesenteric artery flow

measurements has increased rapidly throughout the last decade (Murdoch et al.,2006). Blood flow in the SMA can be measured in a repeatable non - invasive way by the means of color Doppler flowmetry (Iwao et al.,1996).

This study is to investigate the effect of MEN on the blood flow velocities and indices in the SMA in preterm infants utilizing color Doppler flowmetry. The effect of other factors on the SMA blood flow such as gestational age, postnatal age, birth weight, time to feeding, and feeding type is investigated.

PATIENTS AND METHODS

Forty preterm infants were selected for this prospective cohort pretest-posttest study from infants admitted to the neonatal intensive care unit of Al-Zahraa University hospital, during the period from July 2016 to December 2017.

Ethical consideration

1. Ethical approval for this study was obtained from the Department of Pediatrics, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.
2. Written informed consent was obtained from the parents or legal guardians of each enrolled infant.
3. All the data of the patient and results are confidential, and the patient has the right to keep it, the patient guardian has the right to withdraw from the study at any time,
4. The author declared no potential conflict of interest with respect to the research, authorship and publication of this article.
5. The author received no financial support for the research or publication of the article

Inclusion criteria: Stable Preterm Infants with gestational age ranged from 28 to 33 weeks

Exclusion criteria: in this study, infants with clinically apparent congenital abnormalities, infant of diabetic, hypertensive, preeclamptic mothers, evidence of congenital infections, as well as infants born to mothers with clinical chorioamnionitis were excluded. Additionally, infants with sever hemodynamic instability, symptomatic patent ductus arteriosus (PDA), or on vasoconstrictor or vasodilator drugs, as well as those suspected or confirmed NEC, and infants with signs of intestinal obstruction or ileus are also excluded in this study.

Due to strict adherence to the given inclusion and exclusion

criteria, this study was performed over a long time, many preterm infants were ruled out from recruitment. Full history for all infants was taken; which included antenatal, natal and post-natal information, full clinical examinations including estimation of gestational age by Ballard score (**Ballard et al., 1993**), laboratory investigations included complete blood count, serum electrolytes, random blood sugar, blood culture and arterial blood gases. Radiologic investigations were also performed and included plain X-ray of the chest for cardio-respiratory assessment, and plain X-ray of the abdomen to exclude cases with NEC and abdominal ultrasonography.

Trophic feeding in this study utilized minute volumes of breast-milk feeds (BF) ranged from 10 to 15 ml/kg/day (**Dutta et al., 2015**) within 24 to 96 hours of life. In some cases, minute volumes of formula feeds (FF) were utilized due to the lack of maternal milk. In this study, 21 infants were fed by BF, while the other 19 infants were fed by FF. SMA flow velocities were measured utilizing Color Doppler ultra-sonography before trophic feeding, to form baseline data, and after 30 minutes from feeding. Feeding continued

according to feeding protocol of the unit, and infants were monitored for any evidence of feed intolerance including gastric residuals, abdominal girth and intestinal sound or clinical signs of NEC. On the other hand, the time to reach full enteral feeding was observed and recorded.

Infants were divided into categories of two groups considering: gender, gestational age, birth weight, start of feeding, and feeding type to investigate the effect of these factors on the response to feeding and SMA parameter.

Regarding gender, infants were divided into females (n = 18) and males (n = 22). Regarding gestational age, infants were divided into two groups; the first group included infants with gestational age less than 32 weeks (n = 14), while the other group included infants with gestational age greater than or equal 32 weeks (n = 26). Regarding weight at examination, infants were divided into two groups; the first group included infants with weight less than or equal 1.50 kg (small for gestational age) (n = 9), while the other group included infants with weight greater than 1.50 kg (Appropriate for gestational age)

(n = 31). Regarding start of the feeding, infants were divided into two groups; the first one included infants who were fed after 24 hours or less (n = 27), while the other group included infants who were fed later than 24 hours (n = 13).

Regarding feeding type, infants were divided into two groups; the first one included breast-milk fed infants (n = 21), while the other included formula-fed infants (n = 19).

Superior Mesenteric Artery Doppler Flow Velocity Technique

The technique was performed for every hemodynamically stable preterm infants in a supine position. All ultrasound (US) examinations were performed by US scanner (Xaote Lab 50) with linear 7 and 8 MHz research sensors. The testing was performed by the same pediatric radiologist. Color Doppler US in combination with Grey scales US were applied for all the subjects. Flow measurements were repeated three times for each vessel to minimize the errors at least 1 h after their last feeding. When testing with linear 7 MHz sensor,

the superior mesenteric artery was found from branching of the aorta. Its diameter was measured and by applying B regime, anatomic vascular condition was assessed, afterwards, more detailed spectrum blood circulation analysis was performed choosing color Doppler window position in the center of SMA and absolute and derived blood circulation indexes were measured. Absolute indexes were the following: peak systolic velocity (PSV) and End diastolic velocity (EDV). Time average Mean velocity (TAMV) was measured based on these indexes and volumetric blood flow (Vflow) was calculated. Two derivative values were calculated during this test. Pulsatility index (PI) was calculated with Gosling and King formula: $PI = (V_{systole} - V_{diastole}) / V_{mean}$.

Resistive index (RI) was calculated with Pourcelot formula: $RI = (V_{systole} - V_{diastole}) / V_{systole}$. We used warm gel to reduce the patient's movement, trying to minimize discomfort during the procedure to keep his breathing and heart rate steady. (Golzarian et al., 2002).

Table (1): Comparison between SMA flow parameters before and after MEN.

	Range	Mean \pm SD	Median	Paired t-test	
	(Min - Max)			t	p-value
*PSV _b	25.50 - 70.30	53.52 \pm 9.05	55.40	6.936	0.000
*PSV _a	43.70 - 117.10	74.38 \pm 19.26	73.30		
*EDV _b	5.79 - 26.36	13.44 \pm 4.20	12.94	9.953	0.000
*EDV _a	15.48 - 37.18	25.08 \pm 5.46	24.77		
*MV _b	14.96 - 37.54	26.80 \pm 4.62	26.74	8.547	0.000
*MV _a	25.05 - 63.52	41.51 \pm 9.67	40.64		
PI _b	0.89 - 2.13	1.51 \pm 0.30	1.54	-8.471	0.000
PI _a	0.82 - 1.46	1.18 \pm 0.14	1.15		
RI _b	0.56 - 0.88	0.74 \pm 0.08	0.76	-8.778	0.000
RI _a	0.53 - 0.74	0.66 \pm 0.04	0.65		

* Velocities are in (cm/sec) b=before a=after p< 0.05 significant p>0.05 in significant

Table (1) and fig (2) showed that the mean peak systolic velocity after MEN (PSV_a), the mean end diastolic velocity after MEN (EDV_a), and the mean time-average mean velocity after MEN (MV_a) were significantly higher than their corresponding values

before MEN (PSV_b, EDV_b, MV_b). On the other hand, the mean pulsatility index after MEN that, (PI_a), and the mean resistive index after MEN (RI_a) were significantly less than that before feeding (PI_b and RI_b, respectively).

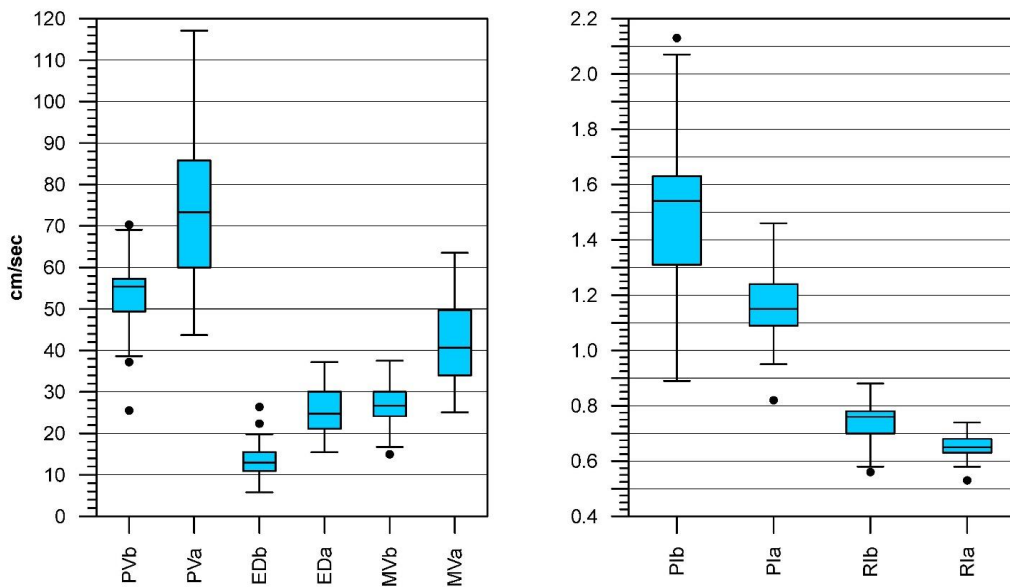


Figure (2): Box plot for SMA blood flow parameters before and after MEN.

Table (2): Comparison between SMA flow parameters after MEN for gender groups.

	Group	Range	Mean ± SD	Median	t-Test		U-Test
		(Min - Max)			t	p-value	p-value
*PSV _a	Female (N 18)	43.70 - 117.10	77.66 ± 20.51	77.85	0.976	0.335	0.325
	Male (N 22)	46.90 - 116.20	71.69 ± 18.20	67.40			
*EDV _a	Female	15.73 - 33.63	26.37 ± 5.09	26.69	1.371	0.178	0.106
	Male	15.48 - 37.18	24.02 ± 5.64	23.18			
*MV _a	Female	25.05 - 59.75	43.47 ± 9.69	44.06	1.164	0.252	0.251
	Male	25.95 - 63.52	39.91 ± 9.57	38.42			
PI _a	Female	0.82 - 1.46	1.16 ± 0.16	1.15	-0.564	0.576	0.492
	Male	0.95 - 1.42	1.19 ± 0.12	1.20			
RI _a	Female	0.53 - 0.74	0.65 ± 0.05	0.65	-0.677	0.502	0.492
	Male	0.58 - 0.73	0.66 ± 0.04	0.67			

* Velocities are in (cm/sec) a=after p<0.05 significant p>0.05 in significant

Table 2 showed that There was no statistical significant difference between males and females regarding SMA velocities (mean peak systolic velocity, mean end diastolic velocity, and mean time-average mean velocity) and indices (mean pulsatility index, and mean resistive index)

Table (3): Comparison between SMA flow parameters after MEN for gestational-age groups.

	Group	Range	Mean ± SD	Median	t-Test		U-Test
		(Min - Max)			t	p-value	p-value
*PSV _a	1 (N 14)	56.90 - 95.10	75.76 ± 12.23	77.90	0.391	0.698	0.510
	2 (N 26)	43.70 - 117.10	73.63 ± 22.34	69.05			
*EDV _a	1	18.21 - 34.32	26.73 ± 4.90	27.22	1.424	0.163	0.138
	2	15.48 - 37.18	24.19 ± 5.63	24.09			
*MV _a	1	31.11 - 52.62	43.07 ± 6.82	44.27	0.747	0.460	0.318
	2	25.05 - 63.52	40.67 ± 10.93	39.46			
PI _a	1	0.82 - 1.42	1.14 ± 0.14	1.15	-1.193	0.240	0.376
	2	0.95 - 1.46	1.20 ± 0.14	1.17			
RI _a	1	0.53 - 0.73	0.65 ± 0.05	0.65	-1.177	0.247	0.361
	2	0.58 - 0.74	0.66 ± 0.04	0.66			

* Velocities are in (cm/sec) a=after group1(<32wks), group 2 (>32 wks.) p< 0.05 significant p>0.05 in significant

Table 3 showed that There was no statistical significant difference between the mean flow velocities and indices of SMA regarding gestational age groups.

Table (4): Comparison between SMA flow parameters after MEN for weight groups.

	Group	Range	Mean \pm SD	Median	t-Test		U-Test
		(Min - Max)			t	p-value	p-value
*PSV _a	1 (N 9)	56.90 - 117.10	88.49 \pm 18.56	85.80	2.690	0.011	0.02
	2 (N 31)	43.70 - 116.20	70.28 \pm 17.69	67.60			
*EDV _a	1	18.21 - 34.32	28.68 \pm 4.60	30.03	2.375	0.023	0.013
	2	15.48 - 37.18	24.03 \pm 5.30	23.59			
*MV _a	1	31.11 - 59.75	48.61 \pm 8.54	48.62	2.697	0.010	0.015
	2	25.05 - 63.52	39.45 \pm 9.08	39.20			
PI _a	1	1.00 - 1.46	1.22 \pm 0.15	1.24	1.075	0.289	0.276
	2	0.82 - 1.42	1.16 \pm 0.14	1.15			
RI _a	1	0.60 - 0.74	0.67 \pm 0.04	0.68	1.077	0.288	0.276
	2	0.53 - 0.73	0.65 \pm 0.04	0.65			

* Velocities are in (cm/sec) a= after group1< 1.5 kg (SGA) group 2>1.5 kg (AGA) p< 0.05 significant p>0.05 in significant

Table 4 showed that the mean flow velocities of the first group were significantly higher than that of the second group. However,

there was no significant difference between the mean indices of the two groups.

Table (5): Comparison between SMA flow parameters after MEN for start-of-feeding groups.

	Group	Range	Mean \pm SD	Median	t-Test		U-Test
		(Min - Max)			t	p-value	
*PV _a	1 N (27)	46.90 - 117.10	79.28 \pm 18.05	79.30	2.468	0.018	0.006
	2 N (13)	43.70 - 116.20	64.19 \pm 18.23	62.00			
*ED _a	1	15.48 - 34.32	26.55 \pm 4.97	27.13	2.641	0.012	0.006
	2	15.73 - 37.18	22.02 \pm 5.33	21.14			
*MV _a	1	25.95 - 59.75	44.13 \pm 8.81	44.62	2.651	0.012	0.005
	2	25.05 - 63.52	36.08 \pm 9.38	34.01			
PI _a	1	0.82 - 1.46	1.19 \pm 0.14	1.18	0.532	0.598	0.588
	2	0.95 - 1.42	1.16 \pm 0.14	1.15			
RI _a	1	0.53 - 0.74	0.66 \pm 0.05	0.66	0.531	0.599	0.568
	2	0.58 - 0.73	0.65 \pm 0.05	0.65			

* Velocities are in (cm/sec) group1 (fed at 24 hours or less) group 2(fed later than 24 hours)
 p< 0.05 significant p>0.05 in significant

Table 5 showed that the mean flow velocities of the first group were significantly higher than that of the second group. However,

there was no significant difference between the mean indices of the two groups.

Table (6): Comparison between SMA flow parameters after MEN for feeding-type groups.

	Group	Range	Mean \pm SD	Median	t-Test		U-Test
		(Min - Max)			t	p-value	p-value
*PSV _a	BF N (21)	49.40 - 116.20	74.84 \pm 16.90	70.50	0.158	0.875	0.789
	FF N (19)	43.70 - 117.10	73.86 \pm 22.04	77.50			
*EDV _a	BF	18.15 - 37.18	25.65 \pm 5.08	25.28	0.698	0.489	0.503
	FF	15.48 - 34.32	24.44 \pm 5.93	24.58			
*MV _a	BF	30.30 - 63.52	42.05 \pm 8.63	41.09	0.367	0.716	0.668
	FF	25.05 - 59.75	40.91 \pm 10.91	40.19			
PI _a	BF	0.82 - 1.38	1.16 \pm 0.14	1.18	- 0.703	0.487	0.957
	FF	1.00 - 1.46	1.19 \pm 0.14	1.15			
RI _a	BF	0.53 - 0.72	0.65 \pm 0.05	0.66	- 0.682	0.499	0.957
	FF	0.60 - 0.74	0.66 \pm 0.04	0.65			

* Velocities are in (cm/sec) a= after group 1 (BF=breast fed)
group 2 (FF=formula fed) p< 0.05 significant p>0.05 in significant

Table 6 showed that there was no statistical significant difference between the mean flow velocities of the two groups, as well as the mean indices.

In this study, the time to reach full enteral feeding (150 -180 ml/kg/day) ranged from 7 days to 20 days with about the same average of 11 days for both weight groups. Three cases (7.5%) developed feeding intolerance and NEC, and they did not survive.

DISCUSSION

Fetal intestine is a relatively dormant organ engaged in minimal activity so that a relative paucity of blood flow and oxygen delivery is adequate to meet its limited oxygen demand. After birth, the intestine experiences a stage of prolific growth and becomes a site of intense metabolic and anabolic activity as it becomes the sole site for

nutrient absorption. This activity necessitates abundant intestinal perfusion and oxygen delivery (**Reber et al., 2002**).

Doppler indices of SMA blood flow velocity and vascular resistance in premature baby before and after trophic feeding were investigated. Results of this study indicated a statistically significant increase in mesenteric blood flow after trophic feeding among the studied neonates indicated by the increased PSV, EDV and MV. Hence, it is suggested that the increment of gut blood flow is affected by trophic feeding among other factors. These findings are in agreement with the findings by **LUCAS et al. (1986)**, who reported that very small, sub nutritional, quantities of enteral food had a potent effect on SMA blood flow, explained by the release of enteroglucagon (a probable trophic hormone for the gut) when they investigated the quantity of enteral feed required to initiate the postnatal surges in plasma enteroglucagon, gastrin, gastric inhibitory polypeptide (GIP), motilin and neurotensin in low birth-weight infants. Also, **Hornum et al. (2006)** showed that Blood flow in the SMA increases after a meal due to a vasoactive effect of the decomposed food. This is supported by **Perko (2001)**

who concluded that food intake induces mesenteric vasorelaxation reflected by a 10-fold increase in the diastolic velocity.

In this study, the mean resistive index (RI) and the mean resistive index (RI) after MEN were significantly lower than that before MEN. Many studies have shown that high resistance patterns of mesenteric arterial Doppler flow study are associated with a significantly reduced tolerance to enteral feeding (**Robel-Tillig et al., 2002**). This resistance reduction causes the nominal rate of intestinal blood flow, and hence oxygen delivery, to be increased during early newborn life. This comes in contrast to the finding of **Reber et al. (2002)**, who reported that, the vascular resistance across newborn intestine significantly decreases in the first few days after birth, secondary to increase in the production of nitric oxide by the endothelium of the blood vessels. Moreover, groups of infants deemed to be at increased risk of NEC tended to have high resistance patterns of flow in the SMA. However, **Coombs et al. (1992)** stated that there is no evidence that high-resistance flow patterns in the splanchnic vessels are associated with a later increased risk of NEC in infants. Also, **Murdoch et al (2006)** concluded that neonates with high

resistance patterns of blood flow velocity in the superior mesenteric artery on the first day of life are at increased risk of developing NEC. As vascular resistance falls, the peak velocities for systole and diastole, as a marker of flow, may increase (Mitchell and Moneta, 2006; Mori et al., 2016).

In this study it was found that the mean flow velocities of the early feeding group were significantly higher than that of the late feeding group. This supported by Morgan et al. (2013) who stated that delaying the introduction of enteral feeds beyond four days after birth will not affect the risk of developing NEC in preterm or very low birth weight infants and may lead to a few days delay in establishing full enteral feeds.

In Conclusion: MEN improve SMA blood flow especially in small for gestational age, thus it might influence the structure and promote development of the premature infant's gastrointestinal tract.

Recommendation: use of early minimal enteral nutrition in premature baby and should be used as an adjunct to parenteral nutrition.

Limitations: this study is a single center study with a small sample

size, and we did not repeat duplex US for documenting more changes with feeding advances (volumetric and caloric).

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تأثير الحد الأدنى من التغذية المعوية على سرعة تدفق الدم بالشريان المساريقي العلوى في الرضع الخدج

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نبذة مختصرة: أثبتت الدراسات أن الحد الأدنى من التغذية المعوية يؤدي الى تحسين نشاط الجهاز الهضمي، وإفراز الهرمونات، وزيادة الحركة والنباتات الميكروبية. ولها أيضاً فوائد إكلينيكية منها تقبل الرضع وخصوصا الخدج للألبان ، ونمواً أكبر في فترة ما بعد الولادة ، وخفض الإنتان المنهجي ، وإقامة أقصر في المستشفى. ولكن لا يعرف سوى القليل عن تأثير الحد الأدنى من التغذية المعوية على سرعة تدفق الدم فى الشرياني المساريقي العلوى في الرضع الخدج.

الهدف من هذه الدراسة: هو الكشف عن التغيرات في تدفق الدم بالشريان المساريقي العلوي الذي يحدث عند الرضع الخدج بعد إعطائهم كمية ضئيلة من التغذية المعوية.

المريض والطريقة: تمت الدراسة على 40 رضيع ناقصي النمو مستقرى العلامات الحيوية عمرهم الجنيني يتراوح من 28 إلى 33 أسبوع وتم اخذ تاريخ مرضى وفحص إكلينيكي مفصل وعمل تحاليل بالدم وأشعة على الصدر والبطن وموجات صوتية على البطن و تم قياس العلامات الدالة على تدفق الدم بالشريان المساريقي العلوى ، وتشمل (سرعة انبساطية نهائية ، وسرعة ذروة انقباضية، متوسط السرعة ومؤشر المقاومة وقابلية النبض) قبل وبعد الحد الأدنى من التغذية المعوية وذلك بواسطة عمل موجات فوق صوتية الدوبلر وتمت الدراسة في وحدة العناية المركزة لحديثى الولادة بمستشفى الزهراء الجامعي خلال الفترة من يوليو 2016 إلى ديسمبر 2017. تم قياس تدفق الدم في جميع الرضع قبل اختبار التغذية وتكراره 30 دقيقة بعد التغذية.

النتائج: أظهرت النتائج انخفاض ذو دلالة إحصائية في مؤشر المقاومة وقابلية النبض بعد 30 دقيقة من إعطاء الحد الأدنى من التغذية المعوية وكان هناك ارتفاعاً ملحوظاً ذو دلالة إحصائية في السرعة الانبساطية والانقباضية والمتوسطة بعد 30 دقيقة من إعطاء الحد الأدنى من التغذية المعوية. ولوحظ أيضاً أن هذا الارتفاع أكثر في الرضع ذوي الأوزان الصغيرة ومن بدؤا الرضاعة مبكراً

الاستنتاج: إعطاء الحد الأدنى من التغذية المعوية للرضع الخدج يحسن الدم في الشريان المساريقي العلوي خاصة في الخدج ناقصي الأوزان ، وبالتالي قد يؤثر على بنية وتعزيز تطوير الجهاز الهضمي قبل الأوان للرضع، ولهذا ننصح بإعطاء الحد الأدنى من التغذية المعوية مبكراً وجنبا لجنب مع التغذية الوريدية.