

SIMULTANEOUS USE OF FACTOR XIII AND FIBRIN DEGRADATION PRODUCTS IN DIAGNOSING EARLY CASES OF NEC AND NEONATAL SEPSIS

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ABSTRACT

Purpose: The study examined the use of factor XIII and fibrin degradation products in diagnosing early cases of NEC and neonatal sepsis.

Methods: Sixty neonates were divided into two groups. 30 preterm neonates suspected with early NEC Diagnosis of NEC was confirmed by modified Bell's score and 30 preterm neonates with symptoms of neonatal sepsis; where sepsis was confirmed by blood culture and CRP. Laboratory evaluation of FDPs and plasma factor XIII was done for all the patients. The study was carried out in a tertiary NICU of the pediatric department, Ain Shams University Hospital. All enrolled neonates had a matched mean birth weight and gestational age. They were either moderate preterms >32 weeks, but <34 weeks, and late preterms >34 weeks, but <37 weeks).

Results: The results indicate a correlation between FDPs and the laboratory data of group B, and it was found out that FDPs were negatively correlated with TLC, Plate-lets, and CRP, reflecting FDPs increase with bone marrow suppression and progression of sepsis. Factor XIII was significantly lower in the group with NEC as compared to the group of sepsis ($p < 0.001$), while FDPs level was significantly higher in the group with sepsis ($p < 0.001$). The correlation between the clinical stages of NEC BELL's score and the level of Initial factor XIII level revealed that the factor level is negatively correlated with stage I of BELL's score. The follow-up revealed that there was no correlation between BELL's score and the level of follow-up factor XIII. On follow-up, the current study demonstrated that TLC, CRP, FDPS, PTT were significantly increased in the sepsis group with p values of 0.021, 0.001, 0.001 and 0.01. The current study found significantly higher partial thromboplastin time (PTT) in the group with sepsis

Conclusion: Factor XIII level can predict early cases of NEC and can differentiate it from neo-natal sepsis.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a fatal gastrointestinal tract inflammatory disease of preterm babies. It is a clinical emergency with high neonatal morbidity and mortality. Early diagnosis and proper treatment are critical. The etiology of NEC is complex and multifaceted, with antenatal hypoxia, ischemia, and postnatal bacterial translocation in the extremely immature

Intestine. In many cases, early symptoms of NEC could not be distinguished from sepsis due to the presence of unstable vital data in both (Schnabl et al., 2008). The severity of the affection determines the outcome, and the mortality rate is inversely related to weight, reaching more than half of the neonates weighing less than 1.5kg, for whom early diagnosis and treatment are required (Macdonald & Green, 2018). An early diagnosis of NEC is required (Lin & Stoll, 2006).

NEC is characterized by severe intestinal inflammation and tissue breakdown that may result in intestinal gangrene. Since there is a great similarity in the clinical presentation of both sepsis and NEC, a new marker would be needed to solve the early diagnostic debate. One promising diagnostic marker is plasma factor XIII (fibrin stabilizing factor), plasma factor XIII is a new modality to differentiate early stages of NEC from late-onset neonatal sepsis. It is believed to have impaired activity in infants with early NEC.

Early detection of NEC necessitates the use of an early laboratory indicator, particularly when combined with a clinical diagnostic and predictive score to improve diagnostic value. NEC is characterized by severe bowel inflammation and tissue breakdown, which can lead to small intestine gangrene. In the setting of bowel tissue inflammation, many markers that increase in response to inflammation were used to diagnose the disease. They involve CRP, serum amyloid-A (SAA), IL-10, and IL-6, and they have a high sensitivity but a low specificity for distinguishing NEC from neonatal sepsis. Other markers, such as I-FABP and claudin-3, can detect intestinal damage with high sensitivity but only late in the course, after the inflammation has progressed, resulting in poor specificity (Evennett et al., 2009; Thuijls et al., 2010; Bizzarro et al., 2014).

Because the clinical manifestations of early stages of sepsis and NEC are so similar, a new marker would be required to resolve the early diagnostic debate. Plasma factor XIII (fibrin stabilizing factor), a clotting factor that plays an important role in the coagulation cascade, is one promising diagnostic marker. Factor XIII is made up of two subunits that are expressed by mesenchymal cells and bone marrow. Following tissue damage, platelet aggregation occurs, resulting in the formation of a blood clot. Plasma factor XIII then stabilizes the fibrin mesh and prevents its breakdown, resulting in the formation of a loose blood clot, recurrent bleeding, and impaired healing. Plasma factor XIII is a novel marker for distinguishing early-stage NEC from late-onset neonatal sepsis. It is thought to have limited activity in infants with early NEC (Landman et al., 1985; Schröder & Kohler, 2013).

METHODOLOGY

Patients and Study Design

In this observational cross-sectional, sixty neonates were divided into two groups: group A (preterm neonates with suspected NEC, n = 30) and group B (preterm neonates with early signs of sepsis, n = 30). The study was carried out in a tertiary NICU of the pediatric department, Ain Shams University Hospital. All enrolled neonates had a matched mean birth weight and gestational age. They were either moderate preterms >32 weeks, but <34 weeks, and late preterms >34 weeks, but <37 weeks).

Exclusion Criteria

Patients with a definitive diagnosis of NEC, gut anomalies, or prior GIT surgery were barred from participating in the study. In addition, due to concomitant homeostatic proteins deficiency very and extremely preterm infants were excluded. Neonates with severe sepsis and septic shock were excluded from the study.

Ethical Approval

This study was approved by the local ethical committee of the pediatric hospital Ain Shams University, Egypt. Written informed consent for all participants was collected from their parents after explaining the aim and the methodology of the study.

A full medical history, thorough general examination with documentation of vital signs (heart rate, blood pressure, respiratory rate, and temperature), activity and complexion, and local examination for abdominal distention, tenderness, intestinal sounds, and discoloration were all performed on all participants. Sepsis and NEC were characterized by the following symptoms: lethargy, decreased activity, and fever, apnea, bradycardia, tachycardia, hypotension, and abdominal distention.

All neonates were monitored for signs of sepsis and feeding tolerance. All neonates were evaluated for feeding tolerance as it is one of the early signs of NEC, which is defined as increased gastric residuals of more than 25% of the previous fed, abdominal distention, unexplained bloody stools, or an X-ray showing bowel wall edema and/or emesis for at least 3 consecutive days, disrupting the feeding plan (Thomas et al., 2018).

Laboratory tests were performed to differentiate between the two diagnoses, where the diagnosis could not be distinguished solely by clinical examination. NEC was confirmed further using Bell's criteria and sepsis was diagnosed using positive blood cultures and clinical suspicion of sepsis. Cases that had progressed to NEC and had a confirmed diagnosis were further subdivided into medically and surgically progressive NEC.

Plain X-ray (gold standard): performed initially on all cases with feeding intolerance, images were serially performed for staging according to Bell's criteria. The study included 30 neonates with a confirmed diagnosis of NEC, while excluding those with feeding intolerance who did not show any radiological signs that supported a NEC diagnosis. A pelvic abdominal ultrasound was performed to assess bowel wall thickness, perfusion, echogenicity, peristalsis, portal venous gas, focal fluid collections, and complex ascites. For up to two weeks of follow-up, clinical examination, X-ray, and pelvic abdominal ultrasound were used to confirm NEC in all participants. The clinical signs of sepsis, as well as elevated C-reactive protein (CRP), were used to make the diagnosis in neonates with identified causative organisms in two blood cultures 48 hours apart.

Hypotension was defined as a mean blood pressure less than 30mmHg.

C.B.C., CRP, blood culture and arterial blood gases are all part of the patient's evaluation. Plasma samples for factor XIII were collected by venous puncture from all patients with feeding intolerance (Bell stage 1) and the matching 30 sepsis control group, then centrifuged and stored until analysis. Samples were brought to room temperature before being tested with ELISA during the analysis. 3 ml samples were collected by venous puncture from all patients with feeding intolerance (Bell stage 1) and the matching 30 sepsis control group, then centrifuged and stored until analysis. Samples were brought to room temperature before being tested with ELISA during the analysis.

Complete blood count was done using KX-21; Sysmex, Kobe (Japan). Semi-quantitative CRP measured by latex agglutination, using kits of Omega Diagnostic Ltd, Alva, (UK). Blood culture: 2 mL of blood was injected into the Bact/ Alert culture bottle under complete aseptic conditions. The inoculated culture bottles were placed in the Bact/ Alert instrument (bio-Mérieux, Marcy l'Etoile, France) as soon as possible, for incubation and monitoring. Positive samples were Gram-stained and subcultured on blood agar, MacConkey agar, and sabouraud dextrose agar supplemented with chloramphenicol (Oxoid, England) and incubated in appropriate temperature (37°C). Full identification of organisms was done with Vitek 2

compact (bio-Mérieux). Coagulase-negative Staphylococcus was identified as a causative pathogen for sepsis by its isolation from two positive blood cultures, according to manufacturer instructions. Measurement of serum levels FDPs and Serum factor XIII was measured by ELISA.

Factor XIII Assay

Citrated plasma samples were isolated by centrifugation for 15 minutes at 4°C. FXIII assay employs the double-sandwich ELISA technique. The pre-coated antibody is a human FXIII monoclonal antibody, and the detecting antibody is a biotin-labeled polyclonal antibody. Following that, Avidin-peroxidase conjugates were added to the wells. After the enzyme conjugate had been thoroughly washed out of the wells with PBS or TBS, the TMB substrate was used for coloration. TMB reacted with peroxidase activity to form a blue product, which then turned yellow after the stop solution was added (Color Reagent C). The target analyte's color intensity and quantity were correlated.

FDPS Assay

FPPs assay was done using Latex Enhanced Immunoturbidimetry Method Assay Kit. This product is used to calculate the concentration of FDP in human plasma. The FDP in human plasma interacts with its corresponding antibody (anti-human FDP antibody) combined with latex particles in a liquid buffer to form an antigen-antibody complex and produce linear turbidity. The turbidity is proportional to the concentration of FDP in the sample and the presence of an appropriate amount of its corresponding antibodies. FDP concentration in a sample can be calculated by comparing the calibrator result with the same processing at a specific wavelength.

Statistical methods: Statistical analysis was carried out using SPSS software (version 20.00). All data were presented as mean, standard error mean, percentage and numbers. P-value was calculated for each risk factor individually for both groups and in correlation with the marker (initially and after 10 days) and to detect the most significant factor affecting the score, a P value less than 0.05 was considered significant. Also, P-value was calculated for each demographic-clinical risk factor and risk factors individually to detect the most significant risk factor affecting the marker level. Furthermore, logistic regression analysis was done for the relationship between factor XIII and NEC while controlling for potential con-founders. Correlation coefficient (r) was done to confirm the linear correlation between the marker and each variable. To determine the sensitivity and specificity of the biomarker.

RESULTS AND DISCUSSION

This study included 60 preterm neonates divided into two groups: group A with suspected NEC (n=30) and group B with suspected late-onset neonatal sepsis (n=30). Demographic and clinical data were displayed in the study (Table 1). Group A had 50 % males and 50 percent females, while Group B had 43.3% males and 56.6 % females(p=0.7). The mean gestational age in group A was 35.8 ± 0.18 but was 35.2 ± 1.3 in group B (p=0.4). The mean birth weight of group A was 2459.1 ± 0.57 g, while the mean birth weight of group B was 2418.4 ± 0.6 g(=0.7)

About 86.6 % of included neonates in group A were delivered by cesarean section (CS), while 80 % of included neonates in Group B were delivered via CS. In terms of feeding, 73.3 % of group A and 66.6 % of group B were breastfed (p=0.5). Hypothermia was found in 60% and 56.6 % of groups A and B, respectively. However, hypotension was found in 40% and 53.3 % of groups A and B. Inotropic drugs were used in 36.6 % and 56.6 % of the groups, A and B, respectively, so there was a significant difference (p=0.01)between the two groups. Metabolic acidosis was found in 76.6 % of group A and 83.3 % of group B, respectively.

Mechanical ventilation was required in 26.6 % of group A and 36.6 % of group B, respectively. Blood cultures were performed 48 hours apart, and the results were initially positive in 3.3 % and 80 % of groups A and B, respectively. Blood cultures were positive after 48 hours in 6.6 % and 73.3 % of groups A and B, respectively ($p < 0.001$).

Regarding routine laboratory data, the mean values of hemoglobin and total leucocyte count (TLC) were significantly lower ($p = 0.005, 0.008$ respectively) in group B than in group A, while CRP was significantly higher ($p < 0.001$) in group B. After seven days follow up, TLC was significantly lower ($p = 0.021$) in group A as compared with group A, On the contrary, CRP was significantly higher ($p < 0.001$) in group B. Specific laboratory evaluation revealed that factor XIII was significantly lower ($p < 0.001$) in the group A as compared to the group B, meanwhile FDPs level was significantly higher ($p < 0.001$) in group B.

The correlation between the demographic data of the included neonates in group A and the baseline factor XIII level revealed that the factor level is correlated negatively ($p = 0.02$) with the length of hospital stay and correlated positively ($p = 0.043$) with the gestational age (Table 3).

The results presented in Table 4 indicated that baseline FDPs levels in group B correlated negatively ($p < 0.001$) with antibiotics intake. The correlation between the baseline level of factor XIII indicated that factor level correlated negatively ($p = 0.03, 0.028$ respectively) with hemoglobin level and FDPs levels.

The data expressed in Table 5 showed baseline FDPs level in group B correlated negatively ($p = 0.045, 0.007$ respectively) with the TLC and platelets, but correlated positively ($p = 0.005$) with CRP level.

The correlation between the clinical stages of NEC modified Bell's score and the baseline level of factor XIII demonstrated that factor level correlated negatively ($p = 0.043$) with stage I of modified Bell's score. The follow-up revealed that there was no correlation between modified Bell's score and the follow-up factor XIII level (Table 6).

Table 1. Initial demographic and clinical data of both studied groups

		Group A (N= 30)		Group B (N= 30)		P value
		N	%	N	%	
Gender	Male	15	50%	13	43.3%	0.7
	Female	15	50%	17	56.6%	
Gestational age	Mean \pm SD	34.94 \pm 2.3	-	33.91 \pm 3.2	-	0.7
Weight	Mean \pm SD	2459.1 \pm 0.57	-	2418.4 \pm 0.6	-	
Cesarean birth	Positive	26	86.6%	24	80%	0.4
Breast feeding	Positive	22	73.3%	20	66.6%	0.5
Hypothermia	Positive	18	60%	17	56.6%	0.45
Hypotension	Positive	12	40%	16	53.3%	0.07
Metabolic acidosis	Positive	23	76.6%	25	83.3%	0.3
Inotrope	Positive	11	36.6%	17	56.6%	0.01*
Mechanical ventilation	Positive	8	26.6%	11	36.6%	0.74
Heart rate	Tachycardia	13	43.3%	12	40%	0.391
	Bradycardia	10	33.3%	11	36.6%	0.45
Blood Culture proved sepsis	Positive(initially)	1	3.3%	24	80%	0.001*
	Positive(after 48 hours)	2	6.6%	22	73.3%	0.001*

All data are expressed as numbers and percentages. Weight and gestational age are expressed as Mean \pm SD. P-value < 0.05 is significant.

Table 2. Initial and follow up laboratory data in both studied groups

	data		Study group		P-value
			Group A	Group B	
Laboratory initially		HB (g/dL)	18.03 ± 9.74	11.4 ± 5.7	0.005*
		TLC (10 ⁹ /L)	13.6 ± 2.85	5.205 ± 3.12	0.008
		Platelet	348 ± 37.4	526 ± 101	0.159
		CRP	6.47 ± 2.53	39.2 ± 6.47	0.001*
		FDPS(ng/ml)	247.9 ± 451	1038.47 ± 598.455	0.001*
		PT	13.7 ± 1.2	14.2 ± 2.2	0.29
		PTT	34.2 ± 3.1	34.6 ± 2.1	0.66
		Factor XIII pg/ml	88.31 ± 35.16	123.28 ± 12.9	0.001*
Follow up lab 7 days later		HB	12.08 ± 3.74	13.36 ± 2.94	0.5
		TLC	9.8 ± 4.3	23.8 ± 17.9	0.021*
		Platelet	340 ± 137	447 ± 165	0.2
		CRP	13.1 ± 2.1	34.8 ± 17.4	0.001*
		FDPS	30.555 ± 16.37	79.33 ± 19.67	0.001*
		PT	19.18 ± 16.55	16.15 ± 8.04	0.55
		PTT	36.75 ± 7.27	38.14 ± 10.87	0.01*

PTT: Partial thromboplastin time, PT : Prothrombin, HB:hemoglobin, CRP: Creative protein, FDPs: fibrin degradation products, TLC: total leucocyte count. All data are expressed as Mean and SD

*Significant difference at $P < 0.05$, using Mann-Whitney test

Table 3. Bell's score presentation among neonates of group A

	BELL Score done initially				BELL Score after 7 days			
	Stage I N(%)	Stage II N(%)	Stage III N(%)	Stage III N(%)	Stage I N(%)	Stage II N(%)	Stage III N(%)	Stage III N(%)
Caes needed medical treatment	IA 1240%	IIB 826.5%	IIIA 13.3%	IIIB 13.3%	IA 26.6%	IIB 13.3%	IIIA 13.3%	IIIB 0
	IB 620%	IIB 26.6%	IIIB 13.3%	IIIB 13.3%	IB 310%	IIB 310%	IIIB 0	IIIB 0
Cases progressed to surgery	IA -	IIB -	IIIA -	IIIB -	IA -	IIB 13.3%	IIIA 13.3%	IIIB 13.3%
	IB -	IIB -	IIIB -	IIIB -	IB 13.3%	IIB 13.3%	IIIB 13.3%	IIIB 13.3%

All data are expressed as numbers and %

Table 4. Correlation of clinical data with baseline Factor XIII and FDPs level in group A and B respectively

		Baseline Factor XIII level		FDPs
		Group A	Group B	Group B
Weight	(r)	-.100		-0.211
	P value	.598		0.311
Gestational age	(r)	.372		-0.368
	P value	0.043*		0.071
Gender	t	.397		.148
	P value	.115		.572
Length of hospital stay	(r)	-0.714		-0.185
	P value	0.02*		0.376
Antibiotics	(t)	.216		-.781
	P value	.549		.0001*
Mechanical ventilation	t	-.122		0.177
	P value	.520		0.861

*P value < 0.05 is significant

Table 5. Correlation of lab data with baseline Factor XIII and FDPs level in group A and B respectively

Lab data		Factor XIII	FDPs
		Base line level ng/ml	
		Group A	Group B
CRP	(r)	0.148	0.808
	P value	0.571	0.005*
TLC	(r)	0.398	-0.372
	P value	0.116	0.043*
HB	(r)	-0.410	-0.714
	P value	0.03*	0.02*
Platelets	(r)	.216	-0.0501
	P value	.549	0.007*
FDPS	(r)	-0.413	-
	P value	0.028*	-
PTT	(r)	-0.080	-0.393
	P value	0.678	0.117
PT	(r)	0.013	-.122
	P value	0.942	.520

*P value <0.05 is significant

Many tools have been investigated for sensitivity and specificity in the diagnosis of NEC in early stages so, this study was carried out to investigate the diagnostic power of factor of early stages of NEC and differentiating NEC cases from cases of late-onset neonatal sepsis. No sex difference in the incidence of NEC in the current study, also the study by Gephart et al (2-17) demonstrated no sex difference while other studies demonstrated increased incidence among female neo-nates (Berkhout et al., 2018)

The current study demonstrated a greater incidence of NEC among the early preterm babies than older neonates (p=0.04). Another study demonstrated a significantly higher incidence of NEC among preterm babies with low gestational age with a P-value <0.001 and that low gestational age is an important independent risk factor for NEC development and mortality with P-value <0.001 that could be due to increased incidence of blood transfusion, antibiotic intake and umbilical catheterization with low gestational age (Gephart et al., 2017)

Many neonates in the current study were delivered by CS-developed NEC, this comes in concordance with Gephart et al who confirmed that CS is considered a risk factor for NEC incidence (Gephart et al., 2017). However, one study postulated that cesarean section could decrease stress and consequently decrease NEC incidence (Berkhout et al., 2018)

A large proportion of NEC patients had nearly hemodynamic instability that re-quired concomitant inotropic support administration, also Gephart et al reported that hypotension required inotropic support was associated with increased risk of NEC (P= 0.001) (Gephart et al., 2017), however many studies suggested that dopamine infusion is not associated with any increase in cardiac output or superior vena cava flow or superior mesenteric artery blood flow, consequently had no direct effect on the mesenteric blood supply to the intestine (Hentschel et al., 1995; Pearson et al., 1996).

Plasma factor XIII and Bell's s scoring system were evaluated in the enrolled sixty patients as both NEC and neonatal sepsis couldn't be differentiated in early stages due to high similarity in clinical signs. Therefore, a high suspicious index was needed.

Clinical signs of neonatal infection are subtle, nonspecific and indistinguishable from those caused by a variety of neonatal non-infectious disorders, in the current study; both studied groups had hypothermia, hypotension, metabolic acidosis and hemodynamic instability, so a greater proportion of the neonates with sepsis required inotropic support, that created a higher significant statistical difference between both groups.

Group B had a higher significant presentation with positive blood culture, which is supported by the study of Guo-Zhong et al. whose patients' cultures were positive for candida, *Enterococcus faecalis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*, while most of the cultures in the current study were positive for *Klebsiella multiple drug-resistant*(53%), coagulase-negative *Staphylococci* (28%) and *Candida*(1%). Ninety percent of the patients with NEC needed conservative medical treatment, entailing cessation of oral intake, Ryle insertion for gut de-compression and antimicrobial treatment, while 10% progressed NEC and underwent surgical exploration and intestinal resection). In the present work, platelet count was lower in NEC cases, but was not statistically significant ($P=0.159$). On the contrary, another study found a statistically significant difference in platelet count being significantly lower in the NEC group (Tao et al., 2015).

Comparing lab parameters between both groups, the current study showed that hemoglobin and TLC were significantly decreased in the sepsis group, while the CRP was significantly higher in which group compared to the NEC group. Factor XIII was significantly lower in the cases of NEC group than the cases of sepsis group ($P<0.001$), although it was in the normal range (2.6-160 pg/ml), this was in concordance with the study of Guo-Zhong et al who stated that decreased activity of factor XIII among the neonates with NEC ($p=0.008$), confirming the inverse correlation between its level and incidence of NEC (Sharma et al., 2018).

FDPS were found to be significantly higher in neonates with sepsis ($p<0.001$) as compared to group A with NEC, this comes in agreement with many studies that found that FDPs were increased in sick neonates with sepsis (Ersoy et al., 2007; Kinasewitz et al., 2004).

In the current study, FDPs were negatively correlated with TLC, hemoglobin, and platelets in the group of sepsis, this comes in concordance with one study that measured FDPs in neonates with sepsis and found that its levels were correlated with prothrombin time, platelets (Toh et al., 2013).

On follow-up, the current study demonstrated that TLC, CRP, FDPS, PTT were significantly increased in the sepsis group with p values of 0.021, 0.001, 0.001, and 0.01. The current study found significantly higher partial thromboplastin time (PTT) in the group with sepsis, in acceptance with other study found that both Prothrombin time (PT) and PTT were significantly higher in neonates with sepsis (Sharma et al., 2018).

Eight neonates out of the NEC group needed mechanical respiratory support, this comes in agreement with Carter et al. who reported a higher incidence of NEC among preterm babies that needed mechanical ventilation (Carter & Holditch-Davis, 2008).

The current study demonstrated the correlation between FDPs and the laboratory data of group B and found that FDPs were negatively correlated with TLC, Plate-lets, and CRP, reflecting FDPs increase with bone marrow suppression and progression of sepsis.

Group A had a baseline measurement of factor XIII and it was correlated with gestational age, length of hospital stay. while group B; had factor XIII was correlated with intake of antibiotics, reflecting its possible affection by drugs. factor XIII was correlated with stage I of Bell's score in group A; indicating its early predictive role for NEC occurrence,

Correlating the level of factor XIII with the cases who developed NEC demonstrated that its level was markedly decreased in progressive cases that required further surgical intervention,

this comes in the agreement of one study that confirmed the negative correlation between the factor level and the severity of the NEC disease, although they found no significant difference between surgical and medical NEC (p=0.189) (Tao et al., 2015).

CONCLUSION

Factor XIII level can predict early cases of NEC and can differentiate it from neo-natal sepsis. FDPs are high among neonates with sepsis Andean differentiate early cases of NEC and sepsis.

CONFLICTS OF INTEREST

There are no conflicts of interest

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