Endoscopic Placental Laser Coagulation in Monochorionic Diamniotic Twins with Type II Selective Fetal Growth Restriction

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Key Words

Monochorionic twins · Selective fetal growth restriction · Twin-to-twin transfusion syndrome · Endoscopic laser coagulation

Abstract

Objective: To determine predictors of survival in monochorionic diamniotic twins with selective fetal growth restriction type II (sFGR-II), with or without twin-to-twin transfusion syndrome (TTTS), treated by endoscopic placental laser coagulation. **Methods:** Laser surgery was performed at 20 (15–27) weeks' gestation in 405 cases of sFGR-II with and 142 without coexisting TTTS. Multivariable logistic regression analysis was performed to determine significant predictors of survival to discharge from hospital. **Results:** There was survival of the small twin in 216 (39.5%) and of the large twin in 379 (69.3%) cases. Significant predictors of survival of both the small and larger twin were ductus venosus Doppler findings in the small twin, gestational age at laser and cervical length, but not the presence of TTTS or Doppler findings in the large twin. **Conclusions:** In sFGR-II, survival after laser surgery is primarily dependent on the condition of the small twin.

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Introduction

Selective fetal growth restriction (sFGR), defined by the presence of a $\geq 25\%$ discordance in estimated weight between the fetuses, is observed in 12% of monochorionic diamniotic (MCDA) twin pregnancies [1]. The condition is subdivided into types I, II and III according to the Doppler finding of the end diastolic flow (EDF) in the umbilical artery of the small fetus, which is normal in type I, absent or reversed (AREDF) in type II or intermittent AREDF in type III [2]. Some cases of sFGR are complicated by twin-to-twin transfusion syndrome (TTTS), defined by marked discordance in amniotic fluid volume with the deepest vertical pool of ≤ 2 cm in one sac and ≥ 8 cm before 20 weeks and >10 cm after 20 weeks in the other sac [3, 4]. In TTTS, the severity of the disease is classified as stage I if the Doppler findings in the umbilical artery and ductus venosus of both fetuses are normal and the bladder of the donor is visible, stage II with normal Doppler findings but not visible bladder, stage III with abnormal Doppler findings in either twin and stage IV with presence of ascites or hydrops in either twin [3].

In the management of TTTS, endoscopic laser coagulation of the inter-twin communicating placental vessels

Table 1. Pregnancy characteristics in monochorionic twin pregnancies with sFGR-II following treatment with endoscopic laser surgery in fetuses that survived and those that did not survive

Characteristic	Smaller fetus		Larger fetus	
	alive (n = 216)	dead (n = 331)	alive (n = 379)	dead (n = 168)
Discordance	32.1 (28.1–38.3)*	35.4 (29.9–42.4)	33.8 (28.7–41.6)	34.5 (30.0–39.7)
Coexisting twin-to-twin transfusion				
Yes	161 (74.5)	244 (73.7)	283 (74.7)	122 (72.6)
No	55 (25.5)	87 (26.3)	96 (25.3)	46 (27.4)
Umbilical artery end diastolic flow				
Positive	–	–	340 (89.7)	146 (86.9)
Negative	202 (93.5)	282 (85.2)	37 (9.8)	21 (12.5)
Reversed	14 (6.5)*	49 (14.8)	2 (0.5)	1 (0.6)
Ductus venosus a-wave (n = 516)				
Positive	165 (80.5%)	170 (54.7%)	277 (76.9%)	116 (74.4%)
Negative/reversed	40 (19.5%)*	141 (45.3%)	83 (23.1%)	40 (25.6%)
Year of laser – 1992	15 (10–19)*	14 (8–18)	15 (10–18)*	13 (7–18)
Placental position				
Anterior	108 (50.0)	165 (49.8)	190 (50.1)	83 (49.4)
Posterior	108 (50.0)	166 (50.2)	189 (49.9)	85 (50.6)
Gestation at laser, weeks	20.4 (18.3–23.1)*	19.7 (17.6–22.0)	20.1 (18.0–22.7)	19.7 (17.6–21.9)
Cervical length, mm	31 (27–36)*	30 (25–34)	31 (27–35)*	29 (22–35)
Gestation at outcome, weeks	32.0 (29.8–34.2)*	21.7 (19.1–25.0)	32.1 (29.9–34.6)*	22.2 (19.8–25.4)
Birth weight, g	1,200 (860–1,710)	–	1,674 (1,287–2,100)	–

Values are presented as median (interquartile range) or n (%). * $p < 0.01$.

is the established treatment of choice [4–6]. In type I sFGR without TTTS, expectant management with close monitoring to define the best time of delivery is associated with good perinatal outcome for both twins [2, 7]. In types II and III sFGR without TTTS, there is a high risk of perinatal death and handicap for both twins; the best management, which includes early delivery, cord occlusion of the FGR twin or endoscopic laser surgery, is uncertain because of the small number of reported cases [2, 7–11].

The objectives of this study are to, firstly, examine the outcome of MCDA twins with sFGR type II, with or without coexistent TTTS, treated by endoscopic placental laser coagulation and, secondly, determine predictors of survival of the growth-restricted and appropriately grown for gestational age twins.

Patients and Methods

This study comprised all cases of MCDA twins complicated by sFGR-II, with and without coexisting TTTS, which were treated by endoscopic laser coagulation of the inter-twin communicating placental vessels in our fetal medicine centre between 1992, when

we first introduced endoscopic laser surgery [4], and April 2014. Umbilical cord occlusion was not a treatment option for sFGR or TTTS in our centre. In total, there were 556 cases that fulfilled the entry criteria, but 9 were excluded from further analysis because they were lost to follow-up. The study population comprised 547 cases of sFGR-II, including 405 (74%) with coexisting TTTS and 142 (26%) without TTTS. The TTTS was stage III in 385 (95%) cases and stage IV in 20 (5%).

Gestational age was determined by ultrasound measurements of the larger twin, including crown-rump length at <14 weeks [12] and head circumference at ≥14 weeks [13]. Diagnosis of sFGR was based on the demonstration that, firstly, the abdominal circumference at <22 weeks or estimated fetal weight at ≥22 weeks was below the 5th percentile of the appropriate reference range [13–15] and, secondly, the inter-twin discordance in estimated fetal weight (weight difference divided by the weight of the large twin) was ≥25%. The estimated fetal weight at <20 weeks was derived by the formula by Warsof et al. [16], and at ≥20 weeks it was derived by the formula of Hadlock et al. [14].

Doppler assessment of the umbilical arteries of both twins and classification of the EDF as normal, absent or reversed was carried out in all cases. Doppler assessment of the fetal ductus venosus and classification of the a-wave as positive, negative or reversed was systematically carried out only after 1995 [17].

Endoscopic laser surgery was carried out using a semi-rigid 2.0-mm diameter fetoscope (Karl Storz GmbH, Tuttlingen, Germany) through a 3.3-mm diameter cannula (Cook Medical, Bloomington,

Table 2. Logistic regression analysis for predicting survival of the smaller fetus in monochorionic twin pregnancies with sFGR-II treated with endoscopic laser surgery

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
Degree of discordance – 25, %	0.965	0.946–0.985	0.001	0.973	0.949–0.998	0.032
Coexisting twin-to-twin transfusion						
No (reference)	1.000					
Yes	1.044	0.705–1.545	0.830			
Donor: umbilical artery EDF						
Negative (reference)	1.000			1.000		
Reversed	0.399	0.214–0.742	0.004	0.393	0.196–0.788	0.009
Donor: ductus venosus a-wave						
Positive (reference)	1.000			1.000		
Negative/reversed	0.292	0.194–0.441	<0.0001	0.416	0.265–0.653	<0.0001
Recipient: umbilical artery EDF						
Positive (reference)	1.000					
Negative/reversed	0.993	0.576–1.713	0.981			
Recipient: ductus venosus a-wave						
Positive (reference)	1.000					
Negative/reversed	1.369	0.909–2.061	0.133			
Date of endoscopic laser – 1992	1.042	1.010–1.074	0.008			
Placental location						
Posterior (reference)	1.000					
Anterior	1.006	0.714–1.418	0.972			
Gestational age at laser (weeks)	1.087	1.024–1.155	0.006	1.189	1.103–1.282	<0.0001
Cervical length (mm)	1.031	1.008–1.055	0.007	1.037	1.012–1.063	0.003

OR = Odds ratio; CI = confidence interval.

ton, Ind., USA), which was introduced transabdominally into the sac of the larger twin after the administration of prophylactic antibiotics and local anaesthesia. In the cases of sFGR without TTTS, we did not undertake amniocentesis, as previously described [10]. A 400- μ m diameter Nd:YAG laser fibre (Dornier Med Tech, Wessling, Germany) with a power output of 40 W was used to coagulate the inter-twin communicating placental vessels. In the early 1990s, all vessels crossing the inter-twin membrane were coagulated [4, 5], but from 1999 the technique of selective coagulation was adopted [18] with additional coagulation of the placenta between the coagulated vessels. Subsequently, in the cases with coexisting TTTS, amnioreduction of the polyhydramnios was undertaken through the cannula over a period of 10–15 min to obtain subjective normalisation of the amniotic fluid volume on ultrasonographic examination. After a period of rest for 1–3 h, the patients were discharged home, and follow-up was usually undertaken in the referral hospitals.

Maternal demographic characteristics, ultrasound findings and details of intrauterine intervention were recorded in a database. Pregnancy outcomes were collected into the same database when they became available from the referring hospitals, general practitioners or from the patients themselves.

Statistical Analysis

Data from categorical variables were presented as n (%) and from continuous variables as median and interquartile ranges. The

MCDA pregnancies with sFGR were divided into smaller and larger fetuses, and comparisons between the fetuses alive and dead in each group were carried out using the χ^2 test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. The tests were considered significant at a p value of <0.05 using two-tailed tests.

Logistic regression analysis was used to determine the variables providing a significant contribution in predicting survival of the smaller and larger fetuses. In the analysis, discordance in estimated inter-twin weight was centred at 25%, and experience in laser surgery was centred at 1992, when the first procedure was carried out. Univariable analysis was carried out to examine the individual variables contributing significantly to the survival of sFGR and larger fetuses by assessing their odds ratios and 95% confidence intervals. Subsequently, multivariable logistic regression analysis with backward stepwise elimination was performed to determine which of these variables provided a significant independent contribution in the logistic model. Kaplan-Meier survival analysis was used to examine the effect of ductus venosus Doppler of the FGR-II fetus in determining the proportion of fetuses surviving following endoscopic laser surgery.

The statistical software package IBM SPSS 21.0 (IBM Corp., Armonk, N.Y., USA) was used for data analyses.

Table 3. Logistic regression analysis for predicting survival of the larger fetus in monochorionic twin pregnancies with sFGR-II treated with endoscopic laser surgery

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
Degree of discordance – 25, %	0.999	0.979–1.019	0.930			
Coexisting twin-to-twin transfusion						
No (reference)	1.000					
Yes	1.112	0.737–1.676	0.614			
Donor: umbilical artery EDF						
Negative (reference)	1.000					
Reversed	1.123	0.629–2.004	0.695			
Donor: ductus venosus a-wave						
Positive (reference)	1.000			1.000		
Negative/reversed	0.487	0.331–0.718	<0.0001	0.576	0.377–0.880	0.011
Recipient: umbilical artery EDF						
Positive (reference)	1.000					
Negative/reversed	0.761	0.436–1.329	0.337			
Recipient: ductus venosus a-wave						
Positive (reference)	1.000					
Negative/reversed	0.869	0.562–1.343	0.527			
Date of endoscopic laser – 1992	1.049	1.017–1.082	0.003			
Placental location						
Posterior (reference)	1.000					
Anterior	1.030	0.716–1.481	0.875			
Gestational age at laser (weeks)	1.056	0.990–1.127	0.095	1.132	1.050–1.221	0.001
Cervical length (mm)	1.043	1.019–1.068	<0.0001	1.050	1.025–1.077	<0.0001

Results

The median gestational age at laser surgery was 20 (range 15–27) weeks for both groups of sFGR-II. In the pregnancies with no TTTS ($n = 142$), there was survival of the smaller twin in 55 (38.7%) cases, the larger twin in 96 (67.6%), at least one twin in 102 (71.8%) and both twins in 49 (34.5%) cases; in total, 151 (53.2%) of 284 babies survived. In the sFGR-II pregnancies with coexisting TTTS ($n = 405$), there was survival of the smaller twin in 161 (39.7%) cases, the larger twin in 283 (69.8%), at least one twin in 291 (71.9%) and both twins in 153 (37.7%) cases; in total, 444 (54.8%) of 810 babies survived. The median gestational age at delivery for the survivors was 32 (range 24–41) weeks, and for the intrauterine or post-natal deaths it was 22 (range 16–37) weeks. Of the 595 survivors, 63 (10.6%), 211 (35.5%), 281 (47.2%) and 40 (6.7%) were born at 24–27, 28–31, 32–36 and at ≥ 37 weeks' gestation, respectively.

The pregnancy characteristics of the survivors are compared with those with intrauterine or neonatal death in table 1. In the smaller twins that survived, compared to those who did not survive, there was significantly lower

estimated inter-twin weight discordance, prevalence of reversed EDF in the umbilical artery and negative or reversed a-wave in the ductus venosus, and higher year of laser surgery, gestational age at laser, cervical length before laser and gestational age at delivery. In the larger twins that survived, compared to those who did not survive, there was significantly higher year of laser surgery, cervical length before laser and gestational age at delivery.

Logistic regression analysis demonstrated that significant predictors of the survival of the smaller twin were estimated inter-twin weight discordance, Doppler findings in the umbilical artery and ductus venosus of the smaller twin, year of endoscopic laser surgery, gestational age at laser and cervical length before laser, but not the presence or absence of coexisting TTTS, Doppler findings in the umbilical artery or ductus venosus of the larger twin or placental location (table 2). In the multivariable analysis, the significant predictors of survival were estimated inter-twin weight discordance, Doppler findings in the umbilical artery and ductus venosus of the smaller twin, gestational age at laser and cervical length before laser, but not year of endoscopic laser surgery. Multivariable logistic regression analysis demonstrated that signif-

Fig. 1. Kaplan-Meier survival curve illustrating the proportion of surviving twins in relation to time interval from endoscopic laser surgery. The red line is for the larger twin, the black line is for the smaller twin and the blue line for both twins.

Fig. 2. Kaplan-Meier survival curve demonstrating the effect of negative or reversed a-wave in the ductus venosus of the growth-restricted twin on the proportion of smaller and larger twins surviving after treatment with endoscopic laser surgery. Black lines indicate negative or reversed a-wave and red lines indicate positive a-wave in ductus venosus. Interrupted lines are for the larger twins and solid lines are for the smaller twins.

icant predictors of the survival of the larger twin were Doppler findings in the ductus venosus of the smaller twin, gestational age at laser and cervical length before laser (table 3).

The Kaplan-Meier survival curve illustrating the proportion of surviving twins, irrespective of presence or absence of coexisting TTTS, in relation to time interval from endoscopic laser surgery is shown in figure 1. There was survival of the smaller twin in 216 (39.5%) cases, the larger twin in 379 (69.3%) and both twins in 201 (36.7%) cases. Most deaths occurred within 2 weeks of laser surgery, including 244 (73.7%) of the 331 deaths of the smaller twin and 109 (64.9%) of the 168 deaths of the larger twin.

The survival curves in figure 2 illustrate the relation between the Doppler findings in the ductus venosus of the FGR-II twin and the survival of the smaller and larger twin. Data on ductus venosus Doppler were available for 516 pregnancies. The smaller twin died in 170 (51.2%) of the 335 cases with positive a-wave and in 141 (77.9%) of the 181 cases with negative or reversed a-wave. The larger twin died in 83 (24.7%) of the 335 cases with positive a-wave in the ductus venosus of the FGR-II twin and in 73 (40.3%) of the 181 with negative or reversed a-wave. Death of the smaller twin within 2 weeks of endoscopic laser surgery occurred in 33.4% of cases with positive a-wave in the ductus venosus of the FGR-II twin and in

50.3% of cases with negative or reversed a-wave ($p < 0.001$). The respective values for the larger twin were 12.2 and 23.8% ($p = 0.005$).

Discussion

Principal Findings of This Study

In about 75% of our cases with sFGR-II, there was co-existing severe TTTS. This high percentage of co-existing TTTS may represent selection bias by referring obstetricians because isolated sFGR has only recently been recognised as a condition for referral to specialist fetal medicine units. In the management of sFGR-II by endoscopic laser coagulation of the inter-twin communicating placental vessels, survival is not related to the presence or absence of co-existing TTTS and is observed in about 40% of the smaller twins and 69% of the larger twins. There is survival of at least one twin in 72% of cases, and in total 54% of all babies survive.

Most deaths of both the small and the larger twin occur within 2 weeks of laser surgery, and the rate of such death is related to the Doppler findings in the ductus venosus of the FGR-II twin, gestational age at laser and pre-laser cervical length. The rate of death of the smaller and larger twins is 33 and 12% if the a-wave is positive, and the

Table 4. Reports on elective intrauterine interventions in monochorionic twin pregnancies presenting with sFGR-II with and without coexistent twin-to-twin transfusion syndrome at about 20 weeks' gestation

Management/first author	n	Survival			Delivery, weeks
		small twin	large twin	overall	
<i>Cord occlusion</i>					
Bebbington, 2012 [11]	24	0	21 (87.5%)	21 (43.8%)	–
Chalouhi, 2013 [10]	22	0	20 (90.9%)	20 (45.4%)	31.1
Total	46	0	41 (89.1%)	41 (44.6%)	
<i>Endoscopic placental vessel laser</i>					
No twin-to-twin transfusion					
Quintero, 2001 [9]	8	3 (37.5%)	4 (50.0%)	7 (43.7%)	31.3
Chalouhi, 2013 [10]	23	7 (30.4%)	17 (73.9%)	24 (52.2%)	32.5
Peeva, 2015	142	55 (38.7%)	96 (67.6%)	151 (53.2%)	32.0
Total	173	65 (37.8%)	117 (67.6%)	182 (52.6%)	32.0
Twin-to-twin transfusion					
Chalouhi, 2013 [10]	166	69 (41.6%)	92 (55.4%)	161 (48.5%)	32.5
Peeva, 2015	405	161 (39.7%)	283 (69.8%)	444 (54.8%)	32.3
Total	571	230 (40.3%)	375 (65.7%)	605 (53.0%)	32.4

respective rates increase to 53 and 24% if the a-wave is negative or reversed. The high mortality rate of the FGR-II twin within 2 weeks of laser surgery, which is particularly marked in those with abnormal flow in the ductus venosus, could at least in part be attributed to the interruption of the oxygenated blood supply from the larger to the smaller twin [2]. Death of the larger twin, which is also related to the degree of cardiovascular compromise of the FGR-II twin, could at least in part be the result of miscarriage triggered by the intrauterine presence of the dead fetoplacental unit of the smaller twin.

Limitations of the Study

The main limitation of the study is related to the lack of data on neonatal morbidity and long-term neurodevelopmental outcome. This is mainly because the patients were referred for surgery from other centres, often from other countries, where the subsequent management of the pregnancy and the neonates was undertaken. Nevertheless, comparisons can be made with other studies on the basis of the gestational age at delivery of the survivors after laser surgery, which is the main determinant of prevalence of neonatal cerebral lesions [19] and long-term neurological outcome [20]. Douglas et al. [19] performed neonatal imaging in survivors after endoscopic laser surgery and reported severe cerebral lesions in 18.4, 7.3 and 3.7% of those born at 24–27, 28–31 and ≥ 32 weeks' gestation, respectively. If these figures were applied to our population, the estimated rate of neonatal cerebral lesions would be 6.5%.

Comparison of the Findings with Previous Studies in the Literature

There is general agreement that the treatment of choice for severe TTTS is endoscopic laser coagulation of the inter-twin communicating placental vessels. However, the best management for sFGR-II without coexistent TTTS is uncertain. Gratacos et al. [2] reported that in about 90% of cases there is deterioration in the fetal condition with development of abnormal Doppler findings in the ductus venosus or abnormal fetal heart rate patterns necessitating early delivery or cord occlusion. Ishii et al. [7] described the natural history of the condition in a series of 27 pregnancies with FGR-II diagnosed at <26 weeks' gestation and managed expectantly. There was fetal or neonatal death of the small twin in 48% of cases and of the larger twin in 33%; at 6 months of age, there was evidence of neurological damage in 29% of the surviving smaller twins and in 17% of the larger twins [7]. In a study of 30 cases of sFGR-II diagnosed at a median gestational age of 20 weeks, the intended management was expectant but in 9 cases cord occlusion was carried out because of deterioration in the condition of the FGR twin; all remaining babies survived after delivery at a median gestation of 30 weeks, but in 14% of the small neonates there was evidence of brain damage [2].

The alternative options in the management of sFGR-II are elective cord occlusion of the FGR twin or endoscopic laser coagulation of the inter-twin communicating placental vessels (table 4). Two studies reported on elective

occlusion of the umbilical cord of the FGR-II twin at about 20 weeks' gestation; in the combined data on a total of 46 pregnancies, there was survival of the larger twin in 89% of cases, and therefore the overall survival was 45% with delivery at a median gestational age of 31 weeks [10, 11]. Data on elective endoscopic laser coagulation of placental vessels in FGR-II without coexisting TTTS were provided by 2 previous studies, and the results are similar to those in our study. In the combined data on a total of 173 pregnancies, there was survival of the smaller twin in 38% of cases, of the larger twin in 68%, and the overall survival was 52% with delivery at a median gestational age of 32 weeks [9, 10]. Similar results were obtained in the combined data from a previous study [10] and our data on a total of 571 pregnancies with FGR-II and coexisting TTTS treated by elective endoscopic laser surgery.

Implications for Clinical Practice

In sFGR-II presenting at 28 weeks' gestation with abnormal Doppler findings in the ductus venosus, it would be reasonable to undertake early delivery if there is a good standard of neonatal care. If in such pregnancy the birth weight of the larger twin is on the 50th percentile, the weight of the smaller twin would be at least 25% less, which is equivalent to an average weight at 26 weeks [15].

In the last 20 years, sFGR-II has been identified at the ultrasound examination that is routinely performed at 20 weeks' gestation. Indeed, many cases are now detected earlier because of the widespread uptake of the 11–13 weeks' scan and the policy of following up MCDA twins at 1–2 weekly intervals thereafter [1, 21].

In sFGR-II presenting with abnormal Doppler findings in the ductus venosus at about 20 weeks' gestation, the likely outcome is fetal death of the smaller twin with consequent high risk of death or brain damage in the larger twin. In such cases, the management of choice would be endoscopic laser coagulation of the inter-twin communicating placental vessels or cord occlusion of the FGR twin. The best option would be determined by the wishes of the parents, technical issues in carrying out the procedure and local expertise. In terms of outcome, the two methods are associated with a similar gestational age at delivery and therefore likely risk of handicap. With cord occlusion, compared to laser surgery, it appears that the rate of survival of the larger twin may be higher but the overall survival is lower. However, these conclusions are drawn from the published data on all cases of FGR-II, rather than those with abnormal Doppler findings in the ductus venosus alone [9–11]. In our series of such cases, only 12% of the small twins and 60% of the larger ones

survived. On the assumption that with cord occlusion the survival of the larger twin is not related to the severity of the disease, reflected in the abnormal ductus venosus flow in the small twin, such intervention that sacrifices the small twin could improve the survival of the larger twin to about 90% [10, 11]. If the rationale of this argument is accepted in cases of sFGR-II without TTTS, the same could be applied for cases with coexistent TTTS, and yet there is general agreement that the best option in the management of such cases is endoscopic laser surgery.

In sFGR-II and normal Doppler findings in the ductus venosus at the time of diagnosis at about 20 weeks, the best choice between elective laser surgery, elective cord occlusion or expectant management with subsequent options of early delivery or emergency intrauterine intervention remains uncertain. With expectant management, it is anticipated that in most cases there will be deterioration in the fetal condition leading to fetal death, extreme preterm delivery or the need for emergency intrauterine intervention [2, 7]. It could therefore be argued that elective cord occlusion or laser surgery at about 20 weeks would be preferable. However, in some cases such interventions may be unnecessary because the fetuses could survive to a gestational age at which early delivery can safely be undertaken. The exact proportion that will fall into the groups of early and late deterioration and the method of predicting the speed of such deterioration require further investigation.

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