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Original Research Article

Comparative Study between the Usage of Whole Blood and Whole Blood Reconstituted in Neonatal Hyperbilirubinemia in Exchange Transfusion

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Abstract:

Introduction: Neonatal hyperbilirubinemia (NNH) is an ongoing problem that requires medical attention and hospital readmission in newborns. Approximately 5-10 percent of all newborns require intervention for pathologic jaundice. Exchange Transfusion (ET) is an effective emergency intervention to lower the S. bilirubin (SBR) levels in neonates at high risk of bilirubin encephalopathy.

Aim: To evaluate the efficacy of whole blood and whole blood reconstituted used in Exchange transfusion in NNH due to HDFN (hemolytic disease of newborn).

Materials and Methods: 40 neonates with ABO and Rh (Rhesus) Hemolytic Disease of Fetus and newborn were included in this study and ET was done in both groups either using Whole Blood (WB) or Whole Blood Reconstituted (WBR) being selected by randomization.

Results: In the present study, the efficacy of exchange transfusion between whole blood and whole blood reconstituted among 20 cases of NNH with ABO HDFN revealed improvement in haemoglobin and fall in SBR level was evident in 7 out of 14 cases with WB and in all 8 cases of ABO HDFN with WBR. Improvement in haemoglobin level and a fall in SBR were observed in both groups of Rh HDFN.

Conclusion: In cases of ABO HDFN, better outcome happened with whole blood reconstituted than whole blood alone for exchange transfusion to bring back desired level of Hb and SBR. In cases of Rh HDFN, no difference was observed between WBR and WB groups. However, to avoid failure in achieving the desired results with ET, in cases of ABO HDFN using O Whole blood, it is essential to use "O Whole Blood" with antibody titre less than the critical level. Further, to avoid unexpected exposure to anti-D in cases of Rh HDFN WBR exchange transfusion, it is necessary to use AB plasma only from male donors without the history of prior transfusion.

Keywords: Hyperbilirubinemia, Jaundice, Exchange Transfusion.

Introduction

Neonatal hyperbilirubinemia (NNH) is an ongoing problem that requires medical attention and hospital readmission in newborns and approximately 5-10 percent of all newborns require intervention for pathologic jaundice [1]. SBR have a physiologic role as an antioxidant, elevations of indirect (unconjugated) bilirubin are potentially neurotoxic whereas direct hyperbilirubinemia (conjugated) indicates a potentially serious hepatic disorders or a systemic illness in neonates. In India the incidence of Neonatal hyperbilirubinemia varied from 4.3% to 6.5% of all live born babies [2,3]. Physiological jaundice can occur in neonates with indirect bilirubin of up to 12 mg/dl. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin which happens when SBR level is >7mg/dl. This unconjugated bilirubin is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase. It may also be partly caused by deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)–glucuronyl transferase to form the polar, water- soluble glucuronide of bilirubin [4].

In some neonates, serum level of indirect bilirubin (unconjugated) may raise excessively leading to neurotoxicity (Kernicterus) that might cause death or lifelong neurologic sequelae. Early detection and treatment are important in the prevention of bilirubin induced encephalopathy [5]. Severe jaundice, Kernicterus and other complications of hyperbilirubinemia should be managed by phototherapy or Exchange transfusion (ET). ET is an effective emergency intervention to lower the SBR levels in neonates those who are at high risk of bilirubin encephalopathy [6]. ET is indicated when phototherapy has failed or insufficient to lower total SBR levels. ET removes circulating total plasma bilirubin, removes antibody-coated sensitized neonates red blood cells (RBCs) and mother´s antibodies in plasma in Hemolytic disease of fetus and newborn (HDFN) thereby replaces them with RBCs compatible with maternal serum and provides albumin with new bilirubin binding site [7].

The decision to do exchange transfusion is based on the Total SBR (TSB) value for that postnatal age, level of sickness of the baby, the likely etiology of jaundice, and presence or absence of bilirubin encephalopathy [8].

A double-volume exchange transfusion [Two 85-mL/kg transfusions for full-term neonates and two 100-mL/kg transfusions for very low birth weight (VLBW) neonates] removes approximately 70% to 90% of the circulating red cells and approximately 50% of the total SBR [8]. ET can be performed using different blood components, For Rh isoimmunisation, the best choice would be O negative packed cells suspended in AB plasma. O negative whole blood or cross- matched baby 's blood group (Rh negative) may also be used. For ABO HDFN, O group (Rh compatible with baby) packed cells suspended in AB plasma or O group whole blood (Rh compatible with baby) should be used. In other situations, baby 's blood group should be used. All blood must be cross matched against maternal plasma [9]. Even though NNF [National neonatology Forum] guidelines recommend Whole blood reconstituted as the first choice for exchange transfusion in India, many centers practice whole blood only. The study is aimed to establish the role of whole blood reconstituted for ET in HDFN.

Aim

To evaluate the efficacy of whole blood and whole blood reconstituted used in Exchange Transfusion (ET) in Neonatal hyperbilirubinemia, (NNH) due to HDFN by comparing SBR and hemoglobin values, duration of phototherapy following exchange transfusion.

Materials and Methods

The Cross-sectional study was conducted at Neonatal Intensive Care Unit (NICU) & Blood Bank at Institute of Child Health & Hospital for Children between August 2018 and July 2019. The cases included were term neonates with hyperbilirubinemia, due to HDFN (either ABO or Rh) who underwent exchange transfusion in the NICU at Institute of Child Health & Hospital for Children. The cases were divided into two groups Whole blood (WB) and Whole blood reconstituted (WBR) by randomization. Sample size calculated was 40.

As per the American Academy of Paediatrics guidelines, ET was done in neonates with NNH due to HDFN with whole blood or whole blood reconstituted [9]. Neonate demographic data such as age of the neonate, sex, birth weight, term or preterm, gestational age, APGAR score at 1 min, 5 min, Mode of delivery, history of exclusive breast feeding and cephalhaematoma was recorded for each neonate on the day of presentation. Mother's obstetric history LMP (Last Menstrual period), EDD (Expected date of Delivery), parity, H/o blood transfusion, H/o abortion was taken into account. The blood samples of neonates with hyperbilirubinemia, were subjected for further testing like SBR, CBC, Hematocrit, Reticulocyte count, CRP, Blood culture, Blood grouping and Rh typing, DCT to know the cause of neonatal jaundice. Mother 's blood sample was taken for blood grouping and Rh typing and ICT.

Inclusion criteria

- The study includes the NNH in term babies (> 37 weeks) due to HDFN with indication for exchange transfusion at Institute of Child Health and Hospital for children, Egmore.
- Blood components collected only from male donors with no prior history of blood transfusion.
- Those who are all willing to participate in this study.

Exclusion Criteria

- Neonatal hyperbilirubinemia, other than HDFN.
- Preterm babies less than 37 weeks.
- Those who are not willing to participate in this study.

Informed consent: The study details were completely explained and a written consent obtained from parents/guardian of the neonates in vernacular language and in English.

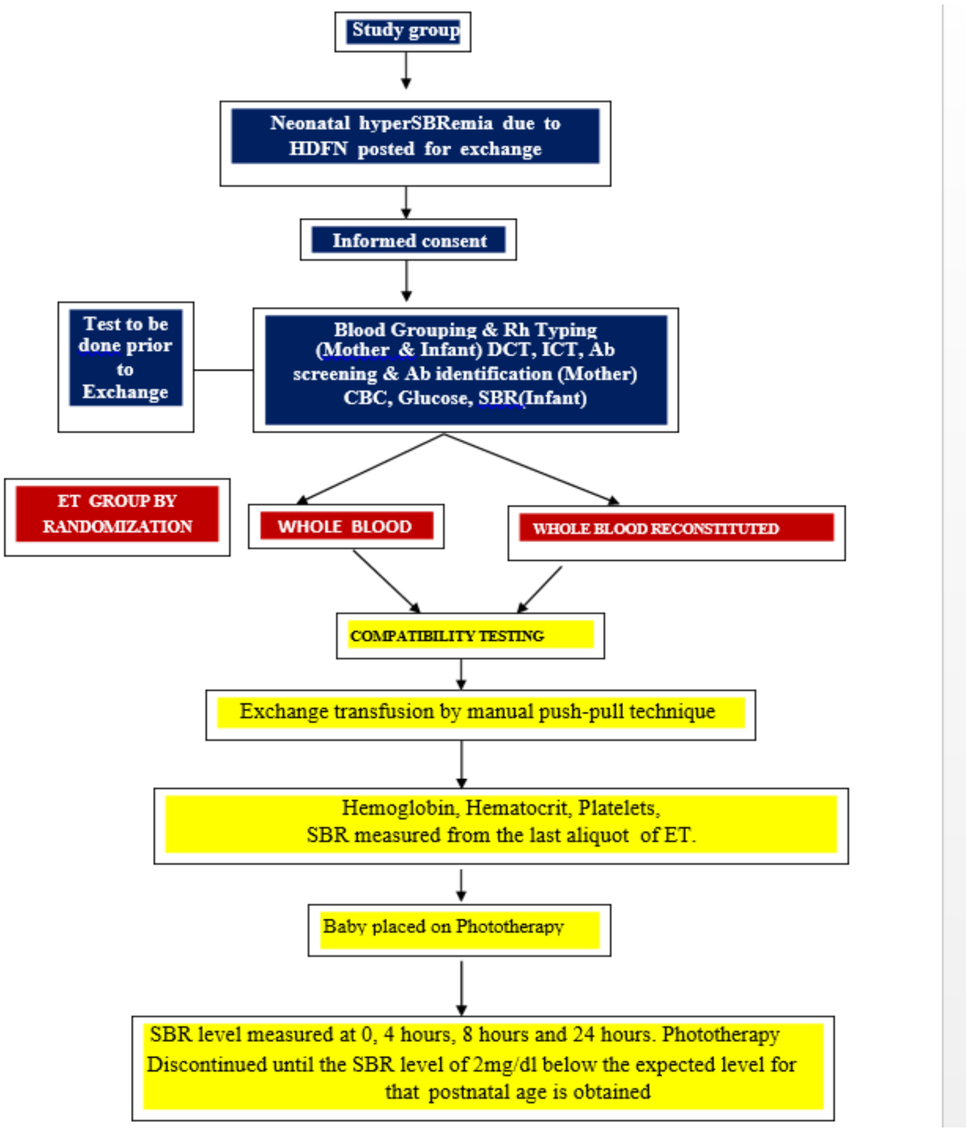

Figure 1:

Mother and Neonatal sample collection procedure: Under aseptic precautions, 2 ml of blood was withdrawn from an appropriate vein by means of 23-gauge needle into EDTA and plain test tubes for the neonate. 10 ml of blood from the mother was withdrawn from antecubital vein by means of 10cc syringe with 18-gauge needle into EDTA and plain test tubes. Serum and red cells were separated by centrifuging at 3000 rpm for 3minutes.

Laboratory tests on infant's blood before exchange Transfusion: The test performed were Hemoglobin (Hb), Hematocrit (Hct), and Platelets (Plt), SBR.

Indications for immediate exchange transfusion in hemolytic disease [10]

- The cord SBR level is >4.5 mg/dL and the cord hemoglobin level are under 11 g/dL.
- The SBR level is rising >1 mg/dL/hour despite phototherapy.
- The hemoglobin level is between 11 and 13 g/dL, and the SBR level is rising >0.5 mg/dL/hour despite phototherapy.
- The SBR level is 20 mg/dL, or it appears that it will reach 20 mg/dL at the rate it is raising.
- There is progression of anemia in the face of adequate control of SBR by other methods.

Preparation for Exchange Transfusion Choice of blood component: In neonate the exchange transfusion was done with either whole blood or whole blood reconstituted [11]. The component of choice in Exchange Transfusion was selected according to NNF guidelines [9].

'Rh' isoimmunization

- ➢ Negative packed cells suspended in AB plasma.
- ➢ O negative whole blood or cross-matched baby 's blood group (Rh negative) may also be used.

'ABO' isoimmunization

- O group (Rh compatible) packed cells suspended in AB plasma
- O group whole blood (Rh compatible with baby) should be used.

Other situations

Blood group as that of baby 's should be used. It should be cross matched against maternal plasma.

Preparation of blood products

All blood products were acquired from voluntary donors and underwent routine screening for infectious agents as per guidelines of Food & Drug Administration Government of India.

Operational Definition [12]

Whole blood reconstituted: The conventional approach was to combine O RBCs with the hematocrit levels of 70– 75% (Rh compatible with the neonate) with AB FFP (prepared by platelet rich plasma method) using sterile connecting device to achieve a desired level (50% ± 5%) hematocrit of the final product. Following recombination, the product can be stored at 1˚ to 6˚ C up to 24 hours.

Whole Blood: The whole blood was anti-coagulated with CPDA-1. Additive anticoagulant solutions should be avoided. Whole blood contains 450 ± 45 ml or 350 ± 35 ml of donor blood plus anticoagulant solution. Whole blood has a hematocrit of 30-40 %. Irradiated RBCs, Leuco-depleted RBCs were not used in this study due to limited facilities.

Compatibility Testing: The transfused red cells must be compatible with the mother 's serum since the hemolysis is caused by maternal IgG antibodies that cross the placenta and destroy the fetal red cells. The blood must be cross matched against the mother 's serum using the antiglobulin method that detects IgG antibodies.

Volume of Donor Blood Required: Quantity needed for total procedure = volume for the actual ET plus volume for tubing dead space (usually 25 to 30 mL). Volume of blood for exchange was calculated using an estimate of the neonate 's circulating blood volume:

- Term infants: 85 mL/kg
- Preterm infants: 100 mL/kg

The volume of whole blood or WBR for double volume exchange transfusion was calculated as twice the blood volume of neonate

Volume to be exchanged = 2 × circulating blood volumes

Calculation for whole blood reconstituted:

Total Volume of Packed Cell =Total Volume of WBR × Desired HCT of WBR / HCT of Packed Cell

Total volume of FFP = Total Volume of WBR − Volume of Packed Cell

Statistical Analysis: The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in independent groups the unpaired sample t-test was used. To find the significance in categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact was used. In all the above statistical tools the probability value .05 is considered as significant level.

Results

Present study was conducted to compare the efficacy of Whole Blood with Whole Blood Reconstituted in Exchange Transfusion in 40 cases of NNH due to Hemolytic disease of fetus and Newborn. Out of 40 cases 22 cases belong to ABO HDFN and 18 cases belong to Rh HDFN.

In ABO HDFN cases, by randomization sampling method 14 cases fell on WB group and 8 cases to WBR group whereas in the Rh HDFN cases, 6 cases fell on WB group and 12 cases to WBR group [Table I].

Table 1:

Cases	Number of cases (n=40)	WB	WBR	Percentage
ABO HDFN	22	14	8	55%
Rh HDFN	18	6	12	45%
Total	40	20	20	100%

In 22 cases of ABO HDFN, OA incompatibility was 40.9% (9 cases) and OB was 59.10% (13 cases). In Rh HDFN 6 mothers were A Negative, 5 were B Negative, 1 was AB Negative, and 6 were O Negative [Table 2]. In the 18 cases of Rh HDFN, 17 (94%) cases were not given Rh Immunoglobulin, and one case was given Rh Immunoglobulin. The percentage of LSCS (Lower segment cesarean section) and NVD (Normal vaginal delivery) were 19% and 81% in the ABO HDFN and 56% and 44% in Rh HDFN study group.

Table 2: Blood group Distribution among mothers in Rh and ABO HDFN

Groups	Rh HDFN (n=18)	Percentage
A Negative	6	33%
B Negative	5	28%
AB Negative	1	6%
O Negative	6	33%

Blood groups and gender distribution in neonates: In ABO HDFN, 9 neonates were A positive, 12 were B positive, 1 was B Negative. In Rh HDFN, 5 neonates were A Positive, 5 were B Positive, 1 was AB positive, and 7 belong to O Positive blood group. In the ABO HDFN cases, 7 (31%) were male and 15 (68%) were female cases and in Rh HDFN cases, male and female cases were 9 each. All were term babies and weighed more than 2.5 kg. In ABO HDFN group one case was less than one day old and 21 cases were two to five days old whereas in the Rh HDFN group four cases were less than one day of age and fourteen cases two to five days old.

Table 3 explains the mean day of appearance of jaundice and day of intervention by ET.

Table 3: Age of the newborn, Day of appearance of Jaundice and Day of intervention by ET

Groups	< 1 day	2-5 days	>6 days	Appearance of Jaundice (mean)	Intervention by ET (mean)
ABO (n=22)	1	21	0	2.9±0.3days	3.8 days
Rh (n=18)	4	14	0	2.7±0.5days	3.6 days

With respect to BIND-M score (modified bilirubin-induced neurologic dysfunction) all the cases in both groups (ABO HDFN & Rh HDFN) belong to mild category [scoring 1-4]. The Bind score was calculated with the clinical signs viz., mental status, and muscle tone, cry pattern and eye movements. The SBR level at the onset of jaundice and at the time of ET was provided in the Table 4.

Table 4: SBR level at the onset of jaundice and ET

	Onset of jaundice (mean SBR)	ET (mean SBR)
Rh WB	10.6	25.3
Rh WBR	9.9	22.5
ABO WB	9.6	24.7
ABO WBR	10	23.4

In Rh HDFN improvement in Hb level was seen in all cases of WB and WBR groups, hence no significance was found between the WB and WBR groups in Rh HDFN.

Whereas in ABO HDFN improvement in post Hb and HCT was seen in 7 cases of WB group and in all 8 cases of WBR. A Significance with p value of less than 0.05 was derived between the groups in ABO HDFN for each of the variables (Hb and Hct).

With ET, SBR level was improved in WB and WBR groups of Rh HDFN (no significance between the groups) whereas in ABO HDFN, SBR improved in all cases of WBR group and in only 7 cases of WB group (p- 0.02) [Table 5&6].

Table 5: Comparison of Hb and SBR in WB and WBR groups in Rh HDFN cases

Rh HDFN (n=18)	Nos	Hb in gms (Pre ET)	Hb in gms (Post ET)	SBR in gms (Pre ET)	SBR in gms (Post ET)
WB (n=6)	6	11.8 (10.8-13.4)	13.1 (12.0-13.9)	25.3 (20.9-32.0)	12.2 (10.0-13.0)
WBR (n=12)	12	11.4 (10.4-12.8)	13.0 (12.0-14.0)	22.5 (20.1-27.2)	11.1 (9.5-13.1)

Table 6: Comparison Hb and SBR in of WB and WBR groups in ABO HDFN cases

ABO HDFN (n=22)	Successful/ Unsuccessful	Nos	Hb in gms (Pre ET)	Hb in gms (Post ET)	SBR in gms (Pre ET)	SBR in gms (Post ET)
WB (n=14)	Successful	7	11.6 (10.0-12.6)	12.1 (10.5-13.1)	24.5 (20.0-29.8)	11.9 (11.3-12.5)
	Unsuccessful	7	11.8 (10.7-12.9)	11.7 (10.5-12.8)	24.8 (20.0-29.8)	21.5 (17.3-25.0)
WBR (n=8)	Successful	8	11.9 (11.0-12.5)	13.0 (12.0-14.0)	23.4 (21.0-27.0)	11.0 (9.8-12.7)

Table 7: ABO HDFN- Independent t test on pre and post values of variables between the WB and WBR groups

			Mean	Standard deviation	P-value	Lower bound	Upper bound
Duration of phototherapy	WB	14	25.077	1.037	0.453	-0.7838	1.6876
	WBR	8	24.625	1.6850			
Pre HCT	WB	14	35.308	2.4168	0.588	-2.6606	1.5510
	WBR	8	35.863	1.8958			
Post HCT	WB	14	32.215	2.3028	0.0005	-7.5465	-3.4728
	WBR	8	37.725	1.9077			
Pre Hb	WB	14	11.769	0.8056	0.646	-0.8537	0.5422
	WBR	8	11.925	0.6182			
Post Hb	WB	14	10.738	0.7676	0.005	-2.5080	-1.1400
	WBR	8	12.563	0.6523			
Pre SBR	WB	14	24.154	3.2289	0.862	-2.4841	2.9418
	WBR	8	23.925	2.1704			
Post- SBR 0 hr	WB	14	15.746	1.8733	0.703	-1.5814	2.2987
	WBR	8	15.388	2.3522			
Post-SBR 4 hrs.	WB	14	18.054	2.0683	0.087	-0.2609	3.5186
	WBR	8	16.425	1.9039			
Post- SBR 8 hrs.	WB	14	15.946	1.4075	0.020	0.2698	2.8475
	WBR	8	14.388	1.3043			
Post-SBR 24 hrs.	WB	14	11.677	0.4693	0.175	-1.1443	0.2232
	WBR	8	12.138	1.0281			

Discussion

In the present study, the efficacy of exchange transfusion between whole blood (WB) and whole blood reconstituted (WBR) on 22 Neonatal cases of hyperbilirubinemia, with ABO HDFN, improvement in Hemoglobin and fall in SBR level was noted in 7 out of 14 cases of ABO HDFN with WB and in all the 8 cases of ABO HDFN with WBR. Similarly in a study by S.Yigit et al on 381 neonates with neonatal hyperbilirubinemia, secondary to ABO HDFN, had reported improvement in hemoglobin and fall in SBR levels in 162 (54%) neonates with WB exchange transfusion and in all 81(100%) neonates with WBR exchange transfusion [13]. Sharma DC et al in their study on 30 cases of ABO HDFN reported improvement in hemoglobin and fall in SBR levels in 100% of cases with WBR exchange transfusion [14].

The remaining 7 cases of ABO HDFN in WB exchange transfusion group failed to show improvement in Hb and fall in SBR, which might be due to the presence of high titre anti-A and anti-B antibodies in serum of the O whole blood [13]. Nevenka Bujandric et al, in their study on 103 cases of ABO HDFN with neonatal hyperbilirubinemia, reported failure in fall of SBR in 23 cases where WB exchange transfusion was done with O whole blood without assessing the high titre anti-A and anti-B antibodies [15]. According to NNF guidelines, for whole blood exchange transfusion in ABO HDFN neonates with hyperbilirubinemia, the importance of anti-A and anti- B titre in O whole blood was not mentioned [9]. However, according to BCSH guidelines, high titre (512) O whole blood should not be used for exchange transfusion in ABO HDFN with neonatal hyperbilirubinemia [16].

In our study, the principle behind the failure of 7 (50%) cases of ABO HDFN with WB exchange transfusion and 100% success with WBR exchange transfusion point towards possible presence of high titre anti-A and anti-B in O whole blood and absence of anti-A and anti-B in O red cells reconstituted with AB plasma. We observed improvement in hemoglobin level and fall in SBR in all cases of Rh HDFN, where O Rh Negative Whole Blood and O Rh Negative Red Cells with AB Plasma from male donors with no prior history of blood transfusion were used.

In a similar study done by Satyasree Devineni on Rh HDFN cases reported 100% success in bringing back hemoglobin and SBR to normal range by using O Rh Negative Whole Blood exchange transfusion [17]. Sharma DC et al., in their study on 61 cases of Rh HDFN, WBR was used for ET and reported 87% success rate to bring back normal levels of Hb and SBR [7]. In a study by Nevenka Bujandric on 150 cases of Rh HDFN, 123 cases showed desired results after O Rh Negative whole blood transfusion [15].

Conclusion

In our study, we observed a better outcome with reconstituted whole blood than whole blood alone in ET to bring back desired levels of haemoglobin and SBR in ABO HDFN cases. In Rh HDFN, no difference was observed in using WBR and WB in ET, with respect to haemoglobin and SBR levels.

However, to avoid failure to achieve desired results in cases of ABO HDFN using O Whole blood exchange transfusion and as a preventive measure it is essential to use O Whole Blood with antibody titre less than critical level.

Further, to avoid unexpected exposure to anti-D in cases of Rh HDFN WBR exchange transfusion, it is necessary to use AB plasma only from male donors without the history of prior transfusion. For conclusive evidence, it is imperative to do further study on large number of cases.

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