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Chapter 5

Middle cerebral artery peak systolic velocity to predict fetal hemoglobin levels in twin anemia polycythemia sequence

Abstract

Objective:

Our aim was to evaluate the diagnostic accuracy of middle cerebral artery peak systolic velocity (MCA-PSV) Doppler measurements in twin anemia polycythemia sequence (TAPS).

Methods:

In a consecutive cohort of monochorionic twin pregnancies with TAPS between 2005 and 2013 in three European fetal therapy centers, the accuracy to predict anemia and polycythemia of MCA-PSV measured just prior to fetal hemoglobin (Hb) measurement by fetal or cord blood sampling was assessed using 2x2 tables.

Results:

A total of 116 measurements (74 in donors and 42 in recipients) from 43 TAPS cases could be used for analysis. MCA-PSV multiples of the mean (MoM) values correlated well with Hb levels ($R = -0.86$ $P < 0.001$). The sensitivity of the MCA-PSV > 1.5 MoM to predict severe anemia (Hb deficit >5 standard deviations (SD)) in TAPS donors was 94% (95%CI 85-98%), specificity 74% (95%CI 62-83%), positive predictive value 76% (95%CI 65-85%), negative predictive value 94% (95%CI 83-98%). The sensitivity of MCA-PSV < 1.0 MoM to predict polycythemia (Hb >5SD above the mean) in TAPS recipients was 97% (95%CI 87-99%), specificity is 96% (95%CI 89-99%), positive predictive value 93% (95%CI 81-97%), negative predictive value 99% (95%CI 81-97%).

Conclusion:

This retrospective study shows a high diagnostic accuracy of MCA-PSV measurements for abnormal Hb levels in TAPS.

Introduction

Twin anemia polycythemia sequence (TAPS) is caused by chronic inter-twin blood transfusion through few minuscule placental anastomoses leading to large inter-twin hemoglobin (Hb) difference without signs of twin oligo-polyhydramnios sequence (TOPS) [1]. TAPS may occur spontaneously, or after laser treatment for twin-twin transfusion syndrome (TTTS) (post-laser TAPS). Antenatal diagnosis is based on Doppler ultrasound abnormalities showing an increased peak systolic velocity in the middle cerebral artery in the donor twin suggestive of fetal anemia and decreased velocities in the recipient twin suggestive of polycythemia, without signs of TOPS. These findings are often accompanied by a distinct difference in placenta echodensity [1]. Postnatal diagnosis is based on inter-twin Hb difference of ≥ 8g/dL, with at least one of the following: reticulocytosis in the donor with a reticulocyte count ratio ≥ 1.7 or small anastomoses (<1 mm) at the placental surface [2].

Middle cerebral artery peak systolic velocity (MCA-PSV) measurement, a non-invasive test, has become the standard test for the diagnosis of fetal anemia in singletons in a variety of fetal diseases [3]. Normal ranges for MCA-PSV for monochorionic diamniotic twins have been reported by Klaritsch et al. [4]. MCA-PSV measurements in monochorionic twin pregnancies with TAPS have not been evaluated before. The aim of this study was to evaluate the diagnostic accuracy of MCA-PSV measurements in TAPS.

Methods

All TAPS cases, in which fetal or neonatal blood sampling for Hb measurement was done, preceded by a MCA-PSV measurement at most 24 hours prior to the procedure, were included in this retrospective study. Fetal blood sampling was routinely performed in TAPS cases managed with intrauterine blood transfusion or partial exchange transfusion. Neonatal blood samplings for Hb measurements were routinely performed in all TAPS twins at birth. Postnatal blood sampling was done after cord clamping and after the delivery of the placenta. Samples were obtained from the umbilical vein. Cord blood samples were not compared to neonatal blood samples. The study cohort consisted of consecutive cases managed between 2005 and 2013 in three European fetal therapy centers (Leiden University Medical Center, the Netherlands; University Hospitals KU Leuven, Belgium and University Hospital - Centre Medico Chirurgical Obstetrical (CMCO) Strasbourg, France).

TAPS was identified using previously published criteria[1]. In brief, antenatal TAPS was

diagnosed when Doppler ultrasound examination revealed an increase in peak systolic velocity in the middle cerebral artery of >1.5 Multiples of the Median (MoM) in one fetus that coincided with a decreased velocity of <1.0 MoM in the co-twin, in the absence of TOPS. Postnatal TAPS was based on inter-twin Hb difference of ≥ 8g/dL, with at least one of the following: reticulocytosis in the donor with a reticulocyte count ratio ≥ 1.7 or small anastomoses (<1 mm) at the placental surface[1]. Intrauterine treatment was offered in TAPS stage 3 and 4. In TAPS stage 1 or 2, intrauterine treatment was offered in case TAPS was quickly progressing (within days) or other signs of severe anemia not meeting criteria for stage 3 (such as increasing heart size or prehydropic signs) were present.

Hb and MCA-PSV values were retrospectively obtained from the medical records. MCA-PSV was measured according to previously described technique by Mari et al. [5]. MCA-PSV values were recalculated to MoM using the reference ranges for monochorionic diamniotic twin pregnancies described by Klaritsch et al. [4]. In normal singleton pregnancies hemoglobin levels increase with gestation. Reference values for fetal hemoglobin according to gestational age have been published by Nicolaides et al. [6]. Hemoglobin deficit was calculated by the difference between the measured Hb value and the mean value for the corresponding gestational age. The definition of severe anemia and polycythemia was based on previous studies on fetal anemia based on Rhesus alloimmunization [3]. Severe anemia or polycythemia was defined as Hb value of more than 5 standard deviations (SD) below the mean in TAPS donors, and more than 5 SD above the mean in TAPS recipients.

	Fetal blood sampling (n=30)	**Postnatal blood sampling (n=13)**
GA at diagnosis (median)	25 (19-30)	26.5 (19-32)[a]
GA in weeks at cordocentesis (median)	26 (±3)	
GA in weeks at birth (median)	31 (26-34)[b]	30 (27-36)
Delivery mode (caesarean section)	19/25 (76%)[b]	11/13 (85%)
Diagnosis made only after birth		3/13 (23%)

[a] n=10, three were diagnosed after birth
[b] n=25, Termination of pregnancy n=1, Lost to follow-up n=4, including cord occlusion in 3 cases

Table 1: Patient characteristics in fetal blood sampling and postnatal blood sampling

Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA). Correlation between continuous variables was analyzed using Pearson linear regression analysis. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihoodratio were calculated using 2x2 tables and standard

formulas for binominal proportions. To calculate the 95% confidence interval (CI) the Wilson's interval method was used [7].

Results

During the study period, 43 patients were diagnosed with TAPS and met the inclusion criteria. In 31/43 (72%) of the cases, TAPS occurred after laser surgery for TTTS (post-laser TAPS) and 12/43 (28%) were spontaneous TAPS cases. A total of 116 complete sets of both MCA-PSV and Hb measurements were available for analysis. In 55/116 (47%) cases, the Hb measurements were obtained by fetal blood sampling. In the other 61/116 (53%) the MCA-PSV measurements were done within 24 hours before birth and Hb measurements were performed in cord blood at birth. 74 of the 116 (64%) measurements belonged to donors and 42/116 (36%) belonged to recipients. Patient characteristics in fetal and postnatal blood sampling and neonatal outcome in donors and recipients are reported in tables 1 and 2.

	Donor	Recipient	p value
Overall survival [a]	29/41 (71%)	40/41 (98%)	0.002
Birth weight	1370 (±409) [b]	1644 (±441) [c]	0.02
Hemoglobin at birth	8.2 (±3.5) [d]	21.6 (±2.7) [e]	<0.001

[a] n=41, 2 patients lost to follow-up for survival
[b] n=27, 16 neonates lost to follow-up for birth weight
[c] n=28, 15 neonates lost to follow-up for birth weight
[d] n=34, 9 neonates lost to follow-up for hemoglobin at birth
[e] n=36, 7 neonates lost to follow-up for hemoglobin at birth

Table 2: Neonatal outcome in donors and recipients

MCA-PSV measurements and Hb levels were highly correlated, R = -0.86 P < 0.001 (Figure 1). In 16 measurements, the MCA-PSV measurement was above 1.5 MoM but the Hb levels were not below more than 5 SD of the mean. The majority of these measurements (11/16, 69%) were done in fetuses that already received an intrauterine transfusion. The sensitivity of the MCA-PSV measurements in the TAPS donor as a test for Hb levels below 5 SD of the mean was 94% (95%CI 85-98%), specificity was 74% (95%CI 62-83%), the positive predictive value 76% (95%CI 65-85%), negative predictive value 94% (95%CI 83-98%), positive

	Hb-deficit <- 5 SD	Hb-deficit >- 5 SD	Total
MCA-PSV > 1.5 MoM	51	16	67
MCA-PSV < 1.5 MoM	3	46	49
Total	54	62	116

Sensitivity=94% (95%CI 85-98%), specificity=74% (95%CI 62-83%), positive predictive value=76% (95%CI 65-85%), negative predictive value=94% (95%CI 83-98%), positive likelihood ratio=3.66, negative likelihood ratio=0.07

Table 3: MCA-PSV Doppler measurements to predict severe fetal anemia (Hb-deficit below -5 SD of the mean) in TAPS donors.

likely hood ratio is 3.66 and negative likelihood ratio is 0.07 (Table 3). Excluding the measurements done after an intrauterine transfusion, sensitivity was 97% (95%; CI 84-99%), specificity was 79% (95%; CI 59-91%), positive predictive value was 86% (95%CI 71-94%), negative predictive value was 95% (95%CI 76-99%), positive likely hood ratio is 4.65 and negative likelihood ratio is 0.04 (Table 4).

	Hb-deficit <- 5 SD	Hb-deficit >- 5 SD	Total
MCA-PSV > 1.5 MoM	30	5	35
MCA-PSV < 1.5 MoM	1	19	20
Total	31	24	55

Sensitivity=97% (95%CI 84-99%), specificity=79% (95%CI 59-91%), positive predictive value=86% (95%CI 71-94%), negative predictive value=95% (95%CI 76-99%), positive likelihood ratio=4.65, negative likelihood ratio=0.04

Table 4: MCA-PSV Doppler measurements to predict severe fetal anemia (Hb-deficit below -5 SD of the mean) in TAPS donors, measurements prior to IUT

In 5 recipients Hb was measured before birth (as part of partial exchange transfusion). In total 11 measurements were performed. In two cases PET was performed once, in one case twice, in one case three times and in the last case four times. In one recipient (postnatal detected TAPS), MCA-PSV before birth was not below 1.0 MoM but neonatal sample of Hb was above 5 SD of the mean, resulting in a sensitivity of 97% (95% CI 87-99%). Three MCA-PSV measurements in recipients were below 1.0 MoM although Hb levels where less than 5 SD above the mean, which resulted in a specificity of MCA-PSV to predict polycythemia of 96% (95% CI 89-99%). The positive predictive value was 93%(95% CI 81-97%) and the negative predictive value was 99% (95% CI 93-100%), positive likely hood ratio is 25 and negative likelihood ratio is 0.03 (Table 5). The mean of MCA-PSV measurements in recipients was 0.70 (±0.17).

	Hb-deficit > 5 SD	Hb-deficit < 5 SD	Total
MCA-PSV < 1.0 MoM	38	3	41
MCA-PSV > 1.0 MoM	1	74	75
Total	39	77	116

Sensitivity=97% (95%CI 87-99%), specificity=96% (95%CI 89-99%), positive predictive value=93% (95%CI 81-97%), negative predictive value=99% (95%CI 93-100%), positive likelihood ratio=25, negative likelihood ratio=0.03

Table 5: MCA-PSV Doppler measurements to predict severe fetal polycythemia (Hb-deficit above 5 SD of the mean) in TAPS recipients.

Discussion

This is the first study reporting on the diagnostic accuracy of MCA-PSV measurements to predict abnormal fetal hemoglobin levels in TAPS. We found high sensitivities and

specificities of MCA-PSV both for anemia and for polycythemia, confirming the clinical usefulness of this noninvasive test in yet another pregnancy complication.

The most common application of MCA-PSV Doppler measurements is in the management of pregnancies with red cell alloimmunization [3]. Obviously, the pathophysiology underlying the development of fetal anemia in this disease differs completely from anemia in TAPS. Still, the predictive values of the Doppler measurements are remarkably similar in both diseases. Interestingly, just as in alloimmune anemia, the accuracy of MCA-PSV measurements was lower after an intrauterine transfusion was performed [8-10].

Our study is the first to evaluate MCA-PSV measurements for the prediction of fetal polycythemia. Recently, a study on the use of MCA-PSV in neonates showed a similar correlation between low peak systolic velocities and polycythemia [11]. The positive predictive value for TAPS donors was 76% and for TAPS recipients 93%. The lower positive predictive value in donors compared to recipients is mainly due to a reduced accuracy for measurements performed when anemia again developed following an intrauterine transfusion. Using only measurements performed prior to the first transfusion, the positive predictive value increased to 86%.

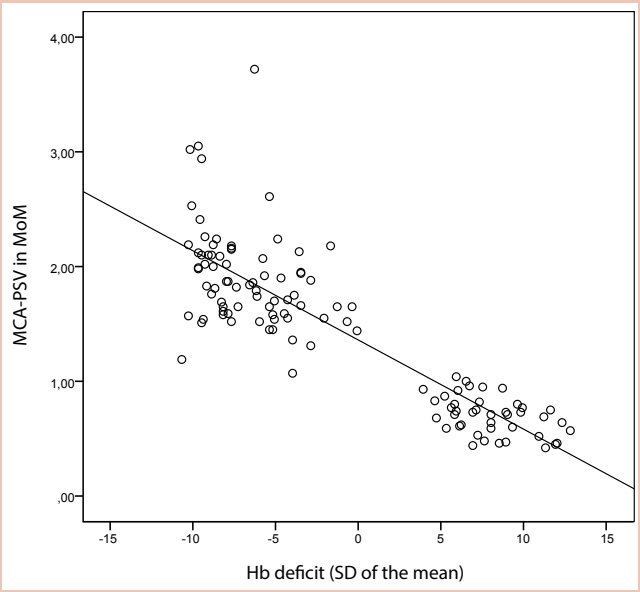

Figure 1. MCA-PSV (MoM) versus Hb deficit (standard deviations (SD) of the mean).
On the x-axis the Hb deficit in SD of the mean. Hb levels below -5 SD are severe anemic donors and Hb above 5 SD are severe polycythemic recipients. On the y-axis Middle cerebral artery peak systolic velocity (MCA-PSV) measurements in multiples of the mean (MoM).

Our results strengthen our previous findings and proposal to use 1.0 MoM as cut-off level for the TAPS recipient, as described in our proposed staging system [1]. With the previously suggested cut-off level of 0.8 MoM, a significant number of cases of severe polycythemia will be missed [12]. As shown in figure 1 there are more outliners in high MCA-PSV measurements compared to low MCA-PSV

measurements. Whether delta MCA-PSV MoM is a more accurate predictor for TAPS should be studied in future research.

One of the limitations of this study is the retrospective nature of this study. The highly selected patient group, referred to specialized centers and predefined as suspected to have TAPS, influences in particular the positive and negative predictive values, since these parameters strongly depend on prevalence. In a general practice with uncomplicated monochorionic twins, MCA-PSV measurements may perform less well. To evaluate the use of MCA-PSV as a screening tool to timely detect TAPS, only large-scale prospective studies in cohorts of monochorionic twins would provide adequate data. Such studies are, apart from being time-consuming and expensive, impossible to perform in specialized fetal therapy centers, given the pre selection of referred high-risk cases. In addition, fetal blood sampling is an invasive procedure with inherent risks, which we cannot perform on a large scale in pregnancies without a strong suspicion for TAPS, thus limiting our ability to confirm negative predictive values.

In summary, in selected pregnancies at increased risk for TAPS, managed in fetal medicine centers, MCA-PSV Doppler is a powerful tool in the prediction of both fetal anemia as well as fetal polycythemia.

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