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INFLUENCE OF FETAL PREDICTORS ON THE QUALITY OF UMBILICAL CORD BLOOD HAEMATOPOIETIC PROGENITOR STEM CELLS

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ABSTRACT

Background: Umbilical cord blood (UCB) serves as a source of progenitor haematopoietic stem cells (HSCs) for transplant and is mainly used to treat blood disorders. The study of fetal factors (antepartum and intrapartum) affecting UCB quality (UCB volume, total nucleated cell count [TNCC] and CD34+ cell count) is imperative to optimize the yield of UCB.

Aim: To study the influence of antenatal and intrapartum fetal factors on the quality of UCB haematopoietic progenitor stem cells (HPSC) (cord blood weight, CD34+ and TNCC) procured at delivery.

Method: A cross-sectional study was conducted involving all women who gave birth in a tertiary public hospital. Antepartum and intrapartum data obtained from the hospital were matched with the quality of UCB as determined by the National Blood Centre, Kuala Lumpur, Malaysia.

Result: Neonatal birth weight has a significant impact on TNCC ($p < 0.05$). A weak, positive association was observed between placental weight and UCB volume, TNCC and CD34+ cell count ($rs = 0.005$, $rs = -0.013$, and $rs = -0.085$, respectively). Conversely, demographic data, gestational age, mode of delivery, gender, and race showed no significant association with the quality of UCB ($p > 0.05$).

Conclusion: Neonatal birth weight is a strong predictor of the quality of UCB. Placental weight and UCB volume, TNCC and CD34+ cell count showed a weak positive correlation; thus, future studies conducted on a larger population are essential to explore other significant predictors to optimize UCB banking.

KEYWORD

Umbilical cord blood (UCB), UCB volume, total nucleated cell count (TNCC), CD34+, fetal factors, antepartum, intrapartum.

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INTRODUCTION

The use of human umbilical cord blood (UCB) as an alternative source for haematopoietic stem cell (HSC) transplantation for a multitude of haematological disorders, immunode ciency syndromes and metabolic disorders commenced more than 30 years ago [1, 2]. Cord blood (CB) serves as a reservoir of multipotent stem cells with superior proliferative capacity to that of cells in marrow or blood from adults. Since the first use of cord blood for transplantation in 1988[1], its popularity as an alternative source of HSC has flourished as UCB offers the advantages of easy procurement, absence of risk for the donor (mother), a reduced risk of transmitted infections, immediate availability of a graft and less stringent criteria for human leukocyte antigen matching without an unacceptably high incidence of graft versus host disease[3,4].

A limiting factor concerning the use of UCB for transplantation is the relatively low number of haematopoietic progenitor stem cells (HPSC) harvested from a single cord blood unit[3] and hence resulted in a delayed haematopoietic recovery. Transplanted UCB grafts have been regarded as satisfactory if they contain at least $1 \times 107 - 3 \times 107$ nucleated cells (NC)/kg recipient weight, with higher doses of cells infused correlating with a shorter time to engraftment[1]. Transplantation-related mortality is associated with the number of NC and CD34+ HSC in the graft: patients who receive a graft containing $< 1.7 \times 107$ CD34+ cells/kg and 1×107 NC cells/kg have a greater

likelihood of mortality. With regard to these observations, the majority of UCB banks have instituted a stringent policy of selecting units with high numbers of total NC and CD34+ cells[5,6].

The total volume of CB collected, total nucleated cell count (TNCC), and CD34+ cell concentration are the main parameters predominantly used to assess the quality of a UCB unit and its potential transplant outcome [7,8].

Thus, the identification of predictors allowing the early discovering of suitable cord blood units would allow a reduction of costs, particularly for the collection, storage and characteristics of cord blood units with insufficient volume or cell numbers.[2,9]

MATERIALS AND METHODS

We performed a cross-sectional study using retrospective secondary data of all newborns delivered by women who had successfully undergone umbilical cord procurement in Serdang Hospital, a tertiary public hospital. A total of 106 cases were obtained from the electronic medical data system. The UCB collected were analysed and stored at the National Blood Centre, Kuala Lumpur.

This study revealed the effect of foetal factors including demographic data, EBW, gestational age, mode of delivery, gender, race, foetal birth weight, and placental weight on the quality of cord blood HPSC (cord blood weight, CD34+ cell count, and TNCC).

Statistical analysis:

The IBM SPSS version 21.0 was used to perform statistical analysis of the data. The normality of data was tested using the Shapiro–Wilk test. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 106 UCB samples were analysed. A simple descriptive analysis of demographic data (birth weight, infant gender, racial background, Apgar score, mode of delivery, and gestational age) are outlined in Table [1]. The percentage and frequency of female infants were higher than those of males at 54.7% (n = 58) and 45.3% (n = 48), respectively. The percentage of full-term births (92.5%, n = 98) was higher than pre-term births (7.5%, n = 8). A total of 95 infants (89.6%) achieved an Apgar score of more than 7, whereas only 11 (10.4%), scored 7 or less. The majority of the newborns were Malay (92.5%, n = 98), followed by Indian (4.6%, n = 5), Chinese (1.9%, n = 2) and other (0.9%, n = 1). The majority of newborns were delivered via spontaneous vertex delivery (SVD, 99%, n = 105) with only 1 infant delivered via lower segment caesarean section (LSCS, 1%). Most infants were estimated to have a birth weight higher than 2 kg (96.3%, n = 102), while the remainder were estimated to have a birth weight of less than 2 kg (3.7%, n = 4). The percentage of infants with normal birth weight was 89.8% (n = 95), which was higher compared to infants with low birth weight, which was 10.2% (n = 11) only.

Table 1. Infant demographic and clinical characteristics

	Frequency (n)	Percentage (%)
Gender		
Male	48	45.3
Female	58	54.7
Ethnicity		
Malay	98	92.5
Chinese	2	1.9
Indian	5	4.6
Other	1	0.9
Mode of Delivery		
Spontaneous Vertex Delivery (SVD)	105	99.0
Lower Segment Caesarean Section (LSCS)	1	1.0
Gestational age		
Pre-term (< 37 weeks)	8	7.5
Full-term (≥ 37 weeks)	98	92.5
Apgar score		
> 7.00	95	89.6
≤ 7.00	11	10.4
Fetal estimated birth weight (FEBW)		
< 2 kg	4	3.7
≥ 2 kg	102	96.3
Infant birth weight		
Low Birth Weight (< 2.7 kg)	11	10.2
Normal (2.7–3.9 kg)	95	89.8

The data distribution of UCB parameters (collected umbilical cord volume, TNCC and CD34+ cell count) are shown in Table [2]. The median and interquartile range for Median and interquartile range were used to represent the distribution of these parameters as there were extreme values in the data.

Table 2. Measures of dispersion of central tendency of UCB parameters

	Median (q1–q2)
Collected Umbilical Cord Volume (g)	137.90 (114.10–211.10)
Total Nucleated Cell Count (TNCC) units	1093.55 (604.08–77865)
CD34+ Cell Count units	2.58 (0.56–11.90)

There was no significant association between antepartum fetal factors including infant gestational age and fetal estimated birth weight (FEBW) with the collected cord blood weight, TNCC, and $CD34^+$ cell count ($p > 0.05$) as shown in Tables 3 and 4.

Table 3. Association between FEBW and quality of umbilical cord blood haematopoietic progenitor stem cells

Parameter	EBW < 2kg (n = 4)		EBW ≥ 2kg (n = 102)		z	p-value
	Median (IQR)		Median (IQR)			
UCB Weight (g)	134.65	(14.03)	138.70	(31.80)	-0.711	0.411
TNCC ($\times 10^6$)	992.72	(368.68)	1096.65	(480.56)	-0.812	0.417
Cd34+ ($\times 10^6$)	2.05	(0.78)	2.70	(2.73)	-1.119	0.263

Table 4. Association between infant gestational age and quality of umbilical cord blood haematopoietic progenitor stem cells

Parameter	Pre-term < 37 weeks (n = 8)		Full-term ≥ 37 weeks (n = 98)		z	p-value
	Median (IQR)		Median (IQR)			
UCB weight (g)	137.90	(28.90)	136.20	(51.00)	-0.110	0.913
TNCC ($\times 10^6$)	1033.60	(470.86)	1027.85	(369.92)	-0.489	0.625
Cd34+ ($\times 10^6$)	4.50	(2.73)	2.03	(1.90)	-1.157	0.247

In addition, fetal intrapartum factors such as infant gender, infant race, Apgar score, and mode of delivery had no significant association ($p > 0.05$) with the quality of umbilical cord blood HPSC (cord blood weight, TNCC and $CD34^+$ cell

count).The single intrapartum factor that showed a significant association with TNCC (p = 0.013, < 0.05) was infant birth weight as presented in Table 5. The median TNCC value for underweight infants (< 2.7 kg) (n = 11) is (947.10 × 10^6) and IQR is (284.13 × 10^6), while the median and IQR for infants of normal weight (2.7–3.9 kg) (n = 58) are 1100.50 × 10^6 and 448.34 × 10^6, respectively. In contrast, birth weight was not significantly associated with cord blood weight or $CD34^+$ cell count (p > 0.05).

Table 5. Association between infant birth weight and quality of umbilical cord blood haematopoietic progenitor stem cells

Parameter	Underweight (< 2.7 kg) (n = 11)		Normal (2.7–3.9 kg) (n = 58)		z	p-value
	Median (IQR)		Median (IQR)			
UCB weight (g)	131.10	(24.90)	139.40	(32.10)	-1.694	0.090
TNCC (×10^6)	947.10	(284.13)	1100.50	(448.34)	-2.486	0.013*
Cd34+ (×10^6)	2.20	(1.81)	2.70	(2.76)	-1.311	0.190

Table 6, reveals that there is a weak positive association between the placental weight and the collected UCB weight (r_s = 0.005), TNCC (r_s = -0.013), and $CD34^+$ cell count (r_s = -0.085).The relationship is statistically insignificant (p values > 0.05).

Table 6. Association between placental weight and quality of umbilical cord blood haematopoietic progenitor stem cells

Parameters	rs	P
UCB weight	0.005	0.969
TNCC (× 10^6)	-0.013	0.924
CD34+ (× 10^6)	-0.085	0.524

DISCUSSION

Cord blood is increasingly finding use as an alternative to bone marrow as a source of stem cells for transplant purposes as it contains a plentiful supply of hematopoietic progenitor cells that have the capacity for renewal. (Nunes & Zandavalli, 2015). The efficacy of an umbilical cord blood unit correlates with its capacity for engraftment following transplantation. Umbilical cord blood banks strive to save cord blood units with its high potency in their stocks (Al-Deghaither, 2015). As such, many studies have been performed worldwide on healthy pregnancies to examine the factors that might influence the yield of TNCC and HSC in UCB. However, this is the only study to concentrate on fetal factors in the Malaysian population in Malaysia.

In this study, 92.5% of the infants delivered in Serdang Hospital between January–June 2014 were full-term. This correlates with the outcome of this study where no significant association between infant gestational age and total nucleated cell count (TNCC) can be observed as a significant association of TNCC can only be found among pre-term babies (Page K. ., 2014). However, infants with a younger gestational age (< 37 weeks) showed a higher $CD34^+$ cell count, although it was not statistically significant (p > 0.05), presented in Table 4. A similar observation was made in a study performed by Page . (2014), but with significant results[10]. A possible explanation may be that the sample size in this study was not large enough to yield a statistically significant difference in collected UCB weight and $CD34^+$ cell count between pre-term and full-term infants. Another interesting revelation by Fadhilah where they did a case-control study in a group of preeclampsia patient. They revealed that gestational age appeared to influence the UCB volume and NCC, but not CD34+ cells among our PE mothers(Abdul Wahid et al., 2012)

Sparrow . (2002) (Sparrow, Cauchi, Ramadi, Waugh, & Kirkland, 2002) showed that vaginal delivery may result in a higher TNCC and increased cord blood recovery [11]. This differs from the findings presented here, as there were no significant associations between the mode of delivery (either SVD or LSCS), and the quality of UCB in terms of cord blood weight, TNCC and $CD34^+$ cell count. This inconsistency may be attributed to the fact that there was only one case of LSCS among this study population of 106.

The current study found that there was no significant association between infant race (Malay, Chinese, and Indian) and the quality of UCB. There are several possible explanations for this result. First, the study sample comprised Asians which differs from the study conducted by Page. (2014) that consisted of Caucasians and African Americans. Furthermore, the parameter followed in the previous study was CFU content, which was not a variable in our study as this parameter is not measured by the National Blood Centre.

The most important clinically relevant finding in this study was an association between infant birth weight and TNCC. This is similar to findings of the study performed by Page ., although there was no significant association between the infant birth weight and other parameters (weight and $CD34^+$ cell count). This is supported by Page . (2014) who did not reveal any statistically significant associations (Page et al., 2014). Placental weight appeared to have a weak positive influence on the quality of UCB in terms of weight, TNCC and $CD34^+$ cell count among our subjects. However, this association was not statistically significant (p > 0.05). This differs from results published by Urcioli. (2009)(Urciuoli et al., 2010), but is consistent with a positive correlation between the placental weight and collected UCB weight. These results are likely related to sample size since our study comprised 106 subjects compared with 365 in Urcioli's study.
In disagreement with previous studies, we did not observe a statistically significant association between the Apgar score and UCB quality (p-values < 0.05). This differs from the study by Askari . (2005) who showed a significant association between Apgar score and UCB quality (Askari, Miller, Chrysler, & McCullough, 2005). This may be attributed to the fact that there were a limited number of infants exhibiting a low Apgar score following delivery in Serdang Hospital; the majority of infants (89.6%) exhibited a score of more than seven. This finding is supportive of the high quality antenatal care offered by the Malaysian Health Services that lowers the frequency of fetal distress in Serdang Hospital: fetal distress during delivery is more likely to yield higher quality UCB (Manegold et al., 2008).

In conclusion, we reveal that neonatal birth weight is a strong predictor of the quality of UCB. Placental weight and UCB volume, TNCC and $CD34^+$ cell count showed a weak positive correlation; thus, prospective studies in a larger population are essential to explore other significant predictors in order to optimize UCB banking.

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REFERENCES

1. Abdul Wahid, F. S., Nasaruddin, M. Z., Idris, M., Razif, M., Tusimin, M., Tumian, N. R., & Abdullah Mahdy, Z. (2012). Effects of preeclampsia on the yield of hematopoietic

stem cells obtained from umbilical cord blood at delivery. Journal of Obstetrics and Gynaecology Research, 38(3), 490-497.
2. Al-Deghaither, S. Y. (2015). Impact of maternal and neonatal factors on parameters of hematopoietic potential in umbilical cord blood. Saudi Med J, 36(6), 704-712. doi:10.15537/smj.2015.6.11247
3. Askari, S., Miller, J., Chrysler, G., & McCullough, J. (2005). Impact of donor- and collection-related variables on product quality in ex utero cord blood banking. Transfusion, 45(2), 189-194. doi:10.1111/j.1537-2995.2004.04117.x
4. Manegold, G., Meyer-Monard, S., Tichelli, A., Pauli, D., Holzgreve, W., & Troeger, C. (2008). Cesarean section due to fetal distress increases the number of stem cells in umbilical cord blood. Transfusion, 48(5), 871-876. doi:10.1111/j.1537-2995.2007.01617.x
5. Nunes, R. D., & Zandavalli, F. M. (2015). Association between maternal and fetal factors and quality of cord blood as a source of stem cells. Rev Bras Hematol Hemoter, 37(1), 38-42. doi:10.1016/j.bjhh.2014.07.023
6. Page, K. M., Mendizabal, A., Betz-Stablein, B., Wease, S., Shoulars, K., Gentry, T., . . . Kurtzberg, J. (2014). Optimizing donor selection for public cord blood banking: influence of maternal, infant, and collection characteristics on cord blood unit quality. Transfusion, 54(2), 340-352. doi:10.1111/trf.12257
7. Sparrow, R. L., Cauchi, J. A., Ramadi, L. T., Waugh, C. M., & Kirkland, M. A. (2002). Influence of mode of birth and collection on WBC yields of umbilical cord blood units. Transfusion, 42(2), 210-215.
8. Urciuoli, P., Passeri, S., Ceccarelli, F., Luchetti, B., Paolicchi, A., Lapi, S., . . . Scatena, F. (2010). Pre-birth selection of umbilical cord blood donors. Blood Transfus, 8(1), 36-43. doi:10.2450/2009.0081-09