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Title

Blood Transfusion Following Major Orthopedic Surgery in Cerebral Palsy – A Retrospective Analysis

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Abstract

Background

Progressive musculoskeletal pathology is ubiquitous among children with cerebral palsy (CP). Corrective surgery places them at risk of major blood loss and red blood cell (RBC) transfusion. Significant variability exists in uptake of peri-operative patient blood management (PBM) strategies. This study aimed to examine factors contributing to RBC transfusion and assist in future development of care pathways.

Methods

A retrospective review at a tertiary paediatric hospital was undertaken to identify patients with CP undergoing either primary spinal fusion or single event, multilevel surgery (SEMLS) between 2010 and 2015. Solely soft tissue procedures were excluded. Data collected included: demographics, Gross Motor Function Classification System (GMFCS) level, surgical details, peri-operative PBM and transfusion rates. Univariable analysis was performed to assess contributing factors to RBC transfusion.

Results

36 spinal fusion and 98 SEMLS patients were included. Pre-operatively, 12% were anaemic, but only 19% had a ferritin checked. Overall, 49 patients (37%) received RBC transfusions. Intra-operative usage of tranexamic acid and cell salvage was 89% and 81% respectively for the spine cohort, and 22% and 3% for the SEMLS cohort. Successively higher GMFCS

levels, sodium valproate usage, longer surgical times, spinal fusion, pelvis instrumentation, and more osteotomies were associated with RBC transfusion.

Conclusion

More than one-third of CP patients that underwent major orthopaedic surgery received RBC transfusion. As expected, the more severely affected patients undergoing longer procedures were at highest risk. Significant improvements can be made in PBM to help optimize patients for surgery and minimize the need for transfusion.

MAIN TEXT

Introduction

Cerebral palsy (CP) results from static neurologic disturbance within the developing brain, and is often associated with progressive musculoskeletal pathology.[1,2] In Australia, the estimated birth prevalence is 2.1 per 1000 live births.[3] Corrective orthopaedic surgery plays an important role in managing the progressive musculoskeletal pathology in CP to help optimize quality of life for patients and their caregivers.[4] Hip dysplasia and scoliosis are common deformities that affect this population, particularly those with more severe functional limitations. Pelvic and/or femoral osteotomies for the hips and spinal fusion for scoliosis are major interventions that are associated with significant risk for large intra-operative blood loss and resultant need for allogeneic red blood cell (RBC) transfusion.[5,6]

The decision to transfuse a child needs to be carefully considered as there are well documented risks associated with RBC transfusion including allergic and haemolytic transfusion reactions, transfusion-transmitted infections, hypothermia, transfusion-associated circulatory overload and transfusion-related acute lung injury .[7-9] Some risks occur relatively

more often in children.[10] Furthermore, the incidence of RBC transfusion is substantially higher in CP patients than in the general population[6,11] because this group is often medically complex and requires more complex surgery.[12-14]

Patient blood management (PBM) refers to evidence-based strategies that aim to improve patient outcomes by identifying and treating peri-operative anaemia, minimizing blood loss and utilizing the appropriate transfusion therapies when necessary.[15] Tranexamic acid (TXA) and cell salvage are current intra-operative tools that are used to minimize intra-operative blood loss and post-operative RBC transfusions.[16,17]

The primary aim of this study was to assess factors associated with allogeneic RBC transfusion in patients with CP undergoing major orthopaedic surgery. There is little literature that directly investigates peri-operative PBM in CP. A recent study by Sherrod et al.[6] investigated blood transfusion incidence and risk factors in paediatric hip dysplasia patients, both with and without neuromuscular disease. We hope that information gained from our study would help clarify current practice patterns, identify high-risk patients, assist in the development of clinical-care pathways, and guide further research in CP.

Methods

A retrospective review was undertaken at a tertiary paediatric hospital with approval from the hospital ethics committee. Hospital procedure codes were used to identify all patients with a primary diagnosis of CP who had undergone a pelvic and/or femoral osteotomy as part of single event, multilevel surgery (SEMLS) or primary posterior spinal fusion between 2010 and 2015. SEMLS patients who only had soft tissue procedures were excluded. Spinal fusion patients with a same-day anterior release were included, but multi-

day staged procedures and revision procedures were excluded. The decision to exclude staged procedures was made to make the groups comparable and statistical analysis consistent using a single pre-operative point.

At our institution, SEMLS procedures were performed by a single consultant surgeon and a senior registrar and/or fellow. Spinal fusions were attended by two consultant surgeons along with a registrar and/or fellow. In all procedures, a consultant anaesthesiologist or a senior fellow would be present.

Demographic data, Gross Motor Functional Classification System (GMFCS) level, medical comorbidities, and peri-operative medical and surgical data, including laboratory values and transfusion data, were collected from each patient's medical record. The primary outcome for analysis was intra- or post-operative allogeneic RBC transfusion. There was no standard protocol for transfusion; hence, the decision to transfuse was clinician dependent.

Statistical analysis

Univariable logistic regression analyses were used to evaluate the strength of associations between pre-operative and surgical variables and intra- or post-operative RBC transfusion as the main outcome. GMFCS level, surgical time, and number of osteotomies were treated as factor variables to ascertain the odds of transfusion for each category relative to the category posing least risk. All statistical analyses were performed using Stata 15.1 (StataCorp 2017, College Station, Texas, USA).

Results

We included a total of 134 children, 98 in the SEMLS cohort and 36 in the primary spinal fusion surgery cohort. Their mean age was 10.1 [SD 3.7] years and 57% were male.

The clinical, surgical, and transfusion details for the two operative groups and the total group are shown in Table 1. In the SEMLS group, all 98 patients underwent a femoral osteotomy, with 15 (15.3%) having additional pelvic osteotomies. The number of osteotomies performed are outlined in Table 1. In the spinal fusion group, instrumentation to the pelvis was performed in 27 (75%) patients and a same-day anterior release was performed in 16 (44%).

A total of 49/134 (37%) patients received a RBC transfusion peri-operatively, 28/98 (29%) of the SEMLS group and 21/36 (58%) of the spinal surgery group. Table 1 shows separate transfusion rates for the intra- and post-operative periods. Altogether, 29 (22%) patients received intra-operative allogenic RBC transfusions, 11 (11%) and 18 (50%) from the SEMLS and spinal surgery groups, respectively. Post-operative RBC transfusions were given to 30 (22.4%) patients in total, 19 (19%) from the SEMLS group and 11 (30%) from the spinal surgery group. Three patients who underwent spinal surgery received three or four units post-operatively.

Post-transfusion haemoglobin (Hb) are seen in Table 1. This was derived by post-operative Hb for patients who only received an intra-operative RBC transfusion and highest Hb value for patients who received a transfusion post-operatively. The average value for both groups is 114.17g/L.

In the SEMLS group, 8/98 (8.2%) patients were not assessed for pre-operative Hb and 76 (77.6%) did not have their ferritin checked. In the spinal surgery group, all 36 patients had a pre-operative Hb performed but only three (8%) had ferritin levels checked. Using our hospital's definition of anaemia, based on age-specific ranges, 16 patients (11.9%) were

anaemic pre-operatively.[18] Intra-operatively, TXA and cell saver were used in more than 80% of spinal surgeries, but less than a quarter of SEMLS (Table 2).

Statistical analysis produced strong evidence that PEG feeding (OR 5.0 [95% CI 2.2, 11.8]), epilepsy (OR 3.4 [95% 1.6, 7.2]), sodium valproate usage (OR 4.3 [95% CI 1.8, 10.0]), spinal fusion vs SEMLS (OR 3.5 [95% CI 1.6, 7.7]), and spinal fusion to the pelvis (OR 3.1 [95% CI 1.4, 6.6]) were all associated with intra- or post-operative transfusion (Table 3).

Successively higher GMFCS levels were also associated with increasingly higher odds of transfusion (relative odds 3.9 [95% CI 0.4, 41.0], 18.8 [95% CI 2.2, 158.5], and 33.0 [95% CI 4.2, 260.3] for levels III, IV and V relative to levels I and II combined). Compared to surgery lasting less than two hours, the relative odds of transfusion was 2.6 [95% CI 0.3, 22.2] for surgeries taking two to five hours and 45.0 [95% CI 3.4, 594.1] for those lasting longer than five hours. Referenced against one osteotomy, the relative odds of transfusion was 6.6 [95% CI 0.8, 53.2] for two osteotomies and 80.0 [95% CI 4.2, 1525.6] for three or more osteotomies.

Discussion

This investigation supports the unsurprising results that longer orthopaedic surgery in increasingly complex patients with CP results in a greater likelihood of receiving intra-operative and/or post-operative allogenic RBC transfusion. GMFCS level was a major contributor to variance in transfusion since higher GMFCS levels are associated with more medical comorbidities, more complex musculoskeletal deformities, and greater surgical complexity.[19] These findings will help guide pre-operative planning and risk stratification in

this patient population and will facilitate further research into PBM in patients with neuromuscular disorders and musculoskeletal deformity.

Sherrod et al.[6] reported a transfusion rate of 31.1% in 517 neuromuscular patients who had hip dysplasia surgery (acetabular and/or femoral osteotomies), a rate comparable to our rate of 37%. These high transfusion rates demonstrate why there needs to be greater attention given to PBM. Both studies identified similar risk factors for transfusion, including pre-operative anaemia, longer operative time, nutritional support through tube feeding, and seizure disorders. We analysed additional peri-operative factors: ferritin levels, use of TXA, and cell salvage.

In this cohort, 10.2% of SEMLS and 16.7% of scoliosis patients were anaemic pre-operatively and therefore at higher risk of mortality, morbidity, and RBC transfusion.[19-21] Faraoni et al.[19] demonstrated the association between pre-operative anaemia, RBC transfusion and increased mortality risk in a study of 51,622 paediatric patients undergoing non-cardiac surgery.

Published guidelines have recommended identifying, investigating, and managing pre-operative anaemia, especially when high blood loss is anticipated.[22,23] Iron deficiency is the most common cause of anaemia in paediatrics and can be present without anaemia.[24] Therefore, it is important that both Hb and ferritin are checked in patients undergoing major surgery where substantial blood loss is anticipated or there is a reasonable risk of RBC transfusion. In this cohort, less than one-third of the SEMLS group and only 8% of the spine fusion group had their ferritin checked. Clearly, improvements can be made in the pre-operative assessment protocol to optimize outcomes for these high-risk patients.

Most of the patients receiving RBC transfusion in this study were not anaemic pre-operatively and anaemia was not found to significantly increase the risk of transfusion. This may be due to the small sample size and the small numbers of patients who were anaemic pre-operatively. The decision to transfuse is often a clinical decision and therefore some of the variance in our results may be due to clinical variation between treating teams and clinicians.

Lacroix et al conducted a randomized controlled trial (TRIPICU study) comparing a Hb transfusion threshold of 70g/L (restrictive-strategy) with 95g/L (liberal-strategy) in 637 critically ill paediatric patients.[25] They found that a restrictive transfusion trigger was safe and associated with fewer RBC transfusions, without an increase in adverse outcomes. While this study did not directly address the CP population, it did study a sample of medically complex children. Subgroup analysis of 124 paediatric general surgery patients from the TRIPICU study by Rouette et al also supports a threshold of 70g/L for stable post-operative patients.[26] Van Popta et al, using a Hb transfusion threshold of 70g/L in their retrospective case series of adolescents undergoing spinal surgery for idiopathic scoliosis, reported that only 4/86 (4.65%) required post-operative RBC transfusion and none required intraoperative transfusion using blood conservation techniques.[27] Recent guidelines addressing indications for transfusion in the paediatric population provide general guidance for peri-operative transfusions and support restrictive transfusion thresholds of 70g/L in stable, non-bleeding patients.[23,28] Whilst the medically complex CP population undergoing complex orthopaedic surgery has not been studied as a stand-alone population, these guidelines provide a framework which can guide decision-making.

TXA has been shown to be effective at reducing intra-operative blood loss and allogenic RBC transfusion rates in spinal corrective surgery, and its use has become common practice at our institution.[29-31] Its value in the other group, however, is less clear.[32] Recently, Bryan et al reported a benefit for TXA in reducing the need for transfusion in patients undergoing periacetabular osteotomies.[16]

Intra-operative cell salvage is another tool to decrease the need for allogenic RBC transfusion.[33] A recent Cochrane review concluded that available evidence supports the use of cell salvage in orthopaedic surgery.[34] Evidence of benefit was stronger for adolescent idiopathic scoliosis surgery, but was less well established for neuromuscular scoliosis.[35-37] Cell salvage for pelvic and femoral osteotomies has also been associated with improvements in post-operative Hb and lower transfusion rates.[38-40] In our cohort, large variation between the two groups on the use of these intra-operative tools (see table 2) highlighting the need for a more consistent approach to PBM.

Multidisciplinary teams involving haematologists, anaesthesiologists, and paediatricians are critical to optimize patient care and assist with complex risk stratification.[41-42] Surgeons may not always be aware of all potential risks, for example, the haemostatic abnormalities associated with the anti-epileptic sodium valproate.[43-44] Input from other teams is beneficial.

Conclusion

Many CP patients undergoing major orthopaedic surgery require peri-operative RBC transfusion, with more severely affected patients undergoing longer procedures being at highest risk. While many patient factors are not modifiable, the data and discussions above

are intended to increase awareness of the need to identify risk factors pre-operatively and to maximise uptake of current PBM guidelines to minimize transfusion rates and improve patient outcomes. PBM guidelines promote standardised transfusion protocols, use of TXA and cell salvage in all patients at risk of needing a transfusion. Evidence is available to guide changes to hospital policies, guidelines, and clinical decision systems. We hope this study encourages readers to review current practice and implement change, as we are doing at our own institution.

Disclosure Statement

All the authors have no disclosures. There are no conflict of interest to declare.

Author Contributions

Lu, MZH: Literature review, acquisition of data, analysis and interpretation of research data, drafting of manuscript

Reid, SM: Analysis and interpretation of research data, drafting of manuscript

Lundine, K: Literature review, conception of research idea, analysis and interpretation of research data, drafting of manuscript

Crighton, G: Literature review, conception of research idea, analysis and interpretation of research data, drafting of manuscript

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Table 1. Clinical, surgical, and transfusion details for the two operative samples.

	SEMLS	**Spinal surgery**	**Total**
	n=98	n=36	n=134
CLINICAL DETAILS			
Male gender, n (%)	60 (61.2)	17 (47.2)	77 (57.5)
Age at surgery, mean years (± SD)	8.8 (± 3.3)	13.8 (± 2.0)	10.1 (± 3.7)
GMFCS level, n (%)			
I	2 (2.0)	0 (0.0)	2 (1.5)
II	23 (23.5)	1 (2.8)	24 (17.9)
III	22 (22.4)	0 (0.0)	22 (16.4)
IV	21 (21.4)	7 (19.4)	28 (20.9)
V	30 (30.6)	28 (77.8)	58 (43.3)
Percutaneous endoscopic gastrostomy	16 (16.3)	16 (44.4)	32 (23.9)
Weight at surgery, mean in kg (± SD)	28.7 (± 13.4)	34.4 (± 10.2)	30.2 (± 12.8)
Weight z-score, mean (± SD)	-0.7 (0.2)	-2.6 (0.3)	-1.2 (0.2)
History of epilepsy, n (%)	42 (42.9)	23 (63.9)	65 (48.5)
Sodium valproate, n (%)	22 (22.4)	8 (22.2)	30 (22.4)
SURGICAL DETAILS			
Surgical time, n (%)			
<2 hr	7 (7.1)	0 (0.0)	7 (5.26)
2-5 hr	91 (92.9)	19 (54.3)	110 (82.71)
>5 hr	0 (0.0)	16 (45.7)	16 (12.03)
Number of osteotomies, n (%)			

1	17 (17.4)	-	-
2	75 (76.5)	-	-
3	5 (5.1)	-	-
4	1 (1.0)	-	-
Pelvic osteotomy, n (%)	15 (15.3)	-	-
Number of spinal levels fused, median (range)	-	16 (6-17)	-
Fusion to pelvis, n (%)	-	27 (75.0)	-
Spinal fusion approach, n (%)			
Posterior only fusion	-	20 (55.6)	-
Anterior release + posterior fusion	-	16 (44.4)	-
BLOOD DETAILS			
Pre-operative			
Hb, mean (± SD)	128.4 (± 10.0)	140.6 (± 16.4)	131.9 (± 13.4)
Anaemia, n (%)	10 (10.2)	6 (16.7)	16 (11.9)
MCV, mean (± SD)	81.7 (± 4.2)	84.7 (± 5.3)	82.6 (± 4.8)
Intra-operative			
Hb, mean (± SD) g/L	107.6 (± 19.2)	97 (± 22.3)	101.6 (± 21.5)
Cell saver return, median mL (range)	220 (150-300)	396 (139-1150)	284 (139-1150)
Number transfused, n (%)	11 (11.2)	18 (50.0)	29 (21.6)
Amount transfused, n (%)			
1 unit	9 (9.2)	12 (33.3)	21 (15.7)
2 units	2 (2.0)	4 (11.1)	6 (4.5)
3 units	0 (0.0)	2 (5.6)	2 (1.5)
Post-operative			

Lowest Hb, mean (± SD) g/L	99.4 (± 15.0)	88.7 (± 14.0)	96.3 (± 15.4)
Number of patients transfused, n (%)	19 (19.4)	11 (30.6)	30 (22.4)
Amount transfused, n (%)			
1 unit	15 (15.3)	7 (19.4)	22 (16.4)
2 units	4 (4.1)	1 (2.3)	5 (3.7)
3 units	0 (0.0)	2 (5.6)	2 (1.5)
4 units	0 (0.0)	1 (2.8)	1 (0.8)
Post-transfusion Hb, mean (± SD) g/L	115.7 +/- 12.7	113.4 +/- 14.9	114.7 +/- 13.6
ICU admission, n (%)	2 (2.0)	27 (75.0)	29 (21.6)
ICU LOS, median days (range)	4 (1-7)	2 (1-24)	2 (1-24)
Total LOS, median days (range)	7 (2-16)	8 (5-128)	7 (2-128)

GMFCS - Gross Motor Function Classification System, Hb – Hemoglobin, SD – Standard deviation, MCV – Mean corpuscular volume, ICU – Intensive care unit, LOS – Length of stay

Table 2. Number of patients obtaining pre-operative blood-work to assess anemia and receiving intra-operative tranexamic acid and/or cell-saver.

	SEMLS n=98	**Spinal surgery n=36**	**Total**
	n (%)	n (%)	n (%)
Pre-operative			
Hb	90 (91.8)	36 (100.0)	126 (94.0)
Ferritin	22 (22.4)	3 (8.3)	25 (18.7)
Intra-operative			
Tranexamic Acid	22 (22.4)	31 (88.6)	53 (39.8)
Cell Saver	3 (3.1)	29 (80.6)	32 (23.9)

SEMLS, single event multi-level surgery, Hb- hemoglobin

Table 3 Results of univariable and multivariable analysis of associations between pre-operative and operative factors and either intra-operative or post-operative transfusion.

	OR [95% CI]	P-value
Age (years)	1.0 [0.9, 1.1]	0.524
Female sex	1.0 [0.5, 2.1]	0.995
GMFCS levels		
I-II	Reference	
III	3.9 [0.4, 41.0]	0.250
IV	18.8 [2.2, 158.5]	0.007
V	33.0 [4.2, 260.3]	0.001
PEG feeding	5.0 [2.2, 11.8]	<0.001
Weight (kg)	1.0 [0.9, 1.0]	0.191
Weight z score	0.8 [0.6, 1.0]	0.060
Sodium valproate for seizures	4.3 [1.8, 10.0]	0.001
Epilepsy	3.4 [1.6, 7.2]	0.001
Pre-operative anemia	1.0 [0.4, 3.1]	0.934
Surgical time (0.5 h increments)	1.5 [1.2, 1.9]	0.001
Surgical time		
<2 hours	Reference	
2-5 hours	2.6 [0.3, 22.2]	0.391
>5 hours	45.0 [3.4, 594.1]	0.004
Spinal vs SEMLS surgery	3.5 [1.6, 7.7]	0.002
Spinal fusion to pelvis	3.1 [1.4, 6.6]	0.004
Number of osteotomies		
1	Reference	

2	6.6 [0.8, 53.2]	0.074
3+	80.0 [4.2, 1525.6]	0.004

OR, odds ratio; GMFCS, Gross Motor Function Classification System; PEG, percutaneous endoscopic gastrostomy; SEMLS, single event multi-level surgery.

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