

Effect of Low-volume Exchange Transfusion on Neonatal Hyperbilirubinaemia: A Retrospective Cohort Study

MANU RAJAN IDICULA¹, KRISHNA KUMAR DIWAKAR², LEELA SUDHAKARAN KAMATH³

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ABSTRACT

Introduction: A double volume exchange transfusion for hyperbilirubinaemia often requires more than one pack of compatible blood to fulfil the calculated volume. This is often unavailable, necessitating exchange transfusion using less than the calculated double-volume. During practice, the authors found that many patients had a positive therapeutic response even when the exchange blood volume was reduced.

Aim: To study the effect of the reduced volume of blood used for exchange transfusion in neonates with hyperbilirubinaemia.

Materials and Methods: A retrospective cohort study was conducted in the Neonatal Intensive Care Unit (NICU), Malankara Orthodox Syrian Church Medical College (tertiary level), Kerala, India, between January 2015 and December 2020. Total 116 patients who underwent exchange transfusion for hyperbilirubinaemia, regardless of gestational age, were included. Pre- and postexchange details, blood chemistry and haemogram were collected from the records and analysed. The patients were grouped into group 1 ($80 \leq 120$ mL/kg) and group 2 ($>120 \leq 160$ mL/kg) based on the volume of blood used for exchange transfusion. The correlation of exchange blood volume

with the percentage drop in bilirubin, rebound rise of bilirubin at six hours, duration of phototherapy, and duration of admission was studied using Pearson's/ Spearman's correlation. Data were statistically analysed using Independent samples t-test, Paired sample t-test, and Chi-square test to determine, if there was a significant difference between the groups.

Results: Out of 116 patients, group 1 had 67 (57.78%) patients, and group 2 had 49 (42.24%) patients. The mean \pm Standard Deviation (SD) gestational age was 37.6 ± 1.57 weeks, and 59 (50.86%) were males. The mean \pm SD postexchange bilirubin was 13.12 ± 3.85 mg/dL in group 1 and 10.26 ± 2.78 mg/dL in group 2, resulting in a bilirubin reduction of $40.74 \pm 12.81\%$ and $53.81 \pm 11.67\%$, respectively. The rebound bilirubin at six hours (13.15 ± 4.32 mg/dL vs 11.23 ± 2.30 mg/dL) made no clinical difference in the management of the patient. The median duration of phototherapy was 48 hours, and the median duration of admission was five days in both groups.

Conclusion: Exchange transfusion with a lower volume of blood, followed by phototherapy, can lead to a clinically acceptable reduction in serum bilirubin. Non availability of the exact 160 mL/kg of blood for exchange is not an adequate reason to delay exchange transfusion.

Keywords: Single volume exchange transfusion, Neonatal Jaundice, Light-emitting diode phototherapy, Serum bilirubin

INTRODUCTION

Exchange transfusion is an intervention that was introduced as early as 1940 to reduce the bilirubin in newborns affected with rhesus haemolytic disease and prevent kernicterus in surviving infants [1,2]. The use of this procedure has since then expanded to the treatment of other conditions such as neonatal sepsis, severe anaemia, polycythaemia, and Disseminated Intravascular Coagulation (DIC) [3-5]. Exchange transfusion removes the antibody-coated red blood cells, products of haemolysis mainly unconjugated bilirubin and replaces them with fresh donor blood. The recommended practice is to perform a double volume (160 mL/kg) exchange for treating hyperbilirubinaemia and a single volume (80 mL/kg) exchange for anaemia [6,7].

It has been reported that the optimum amount of bilirubin was removed when the exchange volume was around 160-180 mL/kg [6]. Over the years, blood banks have started separating and dispensing blood components rather than holding whole blood [8]. Consequently, for exchange transfusion, packed red blood cells suspended in plasma are routinely being used. The usual volume of such a pack is around 300-350 mL [9]. This would mean that when the patient is above 2.3 kg, a single pack would not provide the calculated 160 mL/kg [6].

During clinical practice, the authors encountered situations when only one pack of compatible blood (300-350 mL) was available for conducting the exchange transfusion, which translated to around 100-120 mL/kg of blood and, those patients had an acceptable therapeutic response. The Cochrane analysis comparing a single volume (80 mL/kg) exchange to a double volume exchange concludes that there is insufficient data to change the practice of double volume exchange [10]. However, there is no data on how the treatment is affected when the exchange volume is less than the calculated double volume. The present study is an attempt to fill this gap.

The present study was conducted to evaluate the efficacy of exchange transfusion conducted with less than 160 mL/kg of blood among neonates with hyperbilirubinaemia. The objectives of the study were to find the percentage drop of bilirubin based on the volume of blood used and to determine whether these patients required a longer duration of phototherapy, a greater number of days in admission, and their bilirubin level at discharge.

MATERIALS AND METHODS

A retrospective cohort study was conducted in the tertiary level NICU, Malankara Orthodox Syrian Church Medical College (tertiary level), Kerala, India. The study was approved by the Institutional Ethics Committee (MOSC/IEC/550/2021). The data were collected

between January 2015 and December 2020 and were analysed from May 2021 to August 2021. Confidentiality was maintained at all steps of the study.

Inclusion criteria: All patients who had undergone exchange transfusion for hyperbilirubinaemia, regardless of gestational age during the study period, were included in the study.

Exclusion criteria: Patients who underwent exchange for other indications like sepsis and anaemia were excluded from the study.

Study Procedure

Details of maternal demographics, newborn demographics, Rh/ABO groups, pre-exchange and postexchange bilirubin levels, haemoglobin levels, sodium, potassium, calcium, platelets, reticulocyte count, duration of phototherapy, complications and outcome at discharge were collected from the medical records. Direct antibody tests were performed, and patients were categorised as negative, weak positive, 1+, 2+, 3+ and 4+ [11]. All neonates were given Light Emitting Diode (LED) phototherapy prior to and postexchange transfusion.

Method of exchange: The exchange transfusions were carried out with a two-port (isovolumetric) technique where an umbilical vein or umbilical artery or peripheral artery was used to withdraw blood (out port), while blood was simultaneously transfused using a peripheral intravenous catheter (in port). Compatible, cross-matched, fresh (<seven-day-old) Packed Red Blood Cells (pRBCs) suspended in plasma or whole blood, as per availability, was used for conducting the exchange transfusion.

With 120 mL/kg being the midpoint between a single volume and a double volume exchange, it was taken as a cut-off point for categorising patients into two groups. The analysis was separately done for the two groups: a) exchange blood volume 80 mL/kg to ≤120 mL/kg (group 1); b) exchange blood volume >120 mL/kg to ≤160 mL/kg (group 2). Percentage drop in bilirubin was calculated as (admission bilirubin-postexchange bilirubin) × 100 / admission bilirubin.

STATISTICAL ANALYSIS

Independent samples t-test was performed to determine the difference in the percentage drop of bilirubin between the groups. Paired sample t-tests and Mann-Whitney U tests were performed to check the significant difference between pre-exchange and postexchange serum haemoglobin, electrolytes and platelet values, as the data followed normality. Postexchange complications were analysed for both groups, and a Chi-square test was done to determine if there was a significant difference between the groups. A p-value <0.05 was considered statistically significant, and the entire statistical analysis was performed using R software (EZR).

RESULTS

A total of 131 neonates required exchange transfusion during the period of the study. Among these, 116 patients who underwent exchange transfusion for hyperbilirubinaemia were included in the present study, while 15 (11 with anaemia and 4 with sepsis) were excluded. There were 67 (57.78%) patients (group 1) who received exchange transfusion with a blood volume of 80-≤120 mL/kg and 49 (42.24%) patients (group 2) for whom exchange was done with >120-≤160 mL/kg blood.

The baseline analysis of the groups regarding gestational age, birth weight, gender, place of delivery, mode of delivery, maternal age, Rh incompatibility, ABO incompatibility, and Coombs test status showed no significant difference between the groups, except for birth weight [Table/Fig-1].

| Variables | All subjects N=116 | Group 1 n=67 | Group 2 n=49 | p-value |
|---|-----------------------|-------------------|-----------------|--------------------|
| Gestational age (weeks) | 37.6±1.57 | 37.79±1.49 | 37.41±1.67 | 0.197 ^t |
| Gestational age distribution (in weeks) | | | | |
| GA: 32-33+6 | 2 (1.72) | 1 (1.49) | 1 (2.04) | - |
| GA: 34-36+6 | 19 (16.37) | 10 (14.92) | 9 (18.37) | |
| GA: >37 | 95 (81.89) | 56 (83.58) | 39 (79.59) | |
| Birth weight (kg) | 2.99±0.49 | 3.08±0.38 | 2.87±0.59 | 0.028 ^t |
| Weight at admission (kg) | 2.77±0.49 | 2.84±0.43 | 2.67±0.54 | 0.055 ^t |
| Gender | | | | |
| Male | 59 (50.86) | 37 (55.2) | 22 (44.9) | 0.272 ^c |
| Female | 57 (49.14) | 30 (44.8) | 27 (55.1) | |
| Place of delivery | | | | |
| Outborn | 98 (84.4) | 57 (85.1) | 41 (83.7) | 0.837 ^c |
| Inborn | 18 (15.52) | 10 (14.93) | 8 (16.3) | |
| Mode of delivery | | | | |
| LSCS | 51 (43.97) | 26 (38.8) | 25 (51) | 0.190 ^t |
| VD | 65 (56.03) | 41 (61.2) | 24 (49) | |
| Maternal age (years) | 28.19±4.776 | 28.34±4.98 | 27.98±4.53 | 0.687 ^t |
| Hour of life at admission | 80 (45-120) | 84 (48-120) | 76 (45-120) | 0.5 ^m |
| Weight loss at admission | | | | |
| ≤10% | 80 (69) | 45 (67.2) | 35 (71.4) | 0.624 ^c |
| >10% | 36 (31) | 22 (32.8) | 14 (28.6) | |
| Etiology | | | | |
| Rh incompatibility | 30 (25.86) | 20 (29.9) | 10 (20.4) | 0.251 ^c |
| ABO incompatibility | 34 (29.31) | 19 (28.35) | 15 (30.61) | 0.792 ^c |
| DCT negative | 66 (56.89) | 37 (55.2) | 29 (59.2) | 0.67 ^c |
| DCT positive | 50 (43.10) | 30 (44.78) | 20 (40.81) | |
| DCT weak positive | 8 (6.89) | 3 (4.5) | 5 (10.2) | |
| DCT 1+ | 8 (6.89) | 5 (7.5) | 3 (6.1) | |
| DCT 2+ | 3 (2.58) | 2 (3) | 1 (2) | |
| DCT 3+ | 7 (6.03) | 4 (6) | 3 (6.1) | |
| DCT 4+ | 24 (20.69) | 16 (23.9) | 8 (16.3) | |
| Reticulocyte count (n=110) | 7.02±5.3 | 7.22±5.5 | 6.76±5.15 | 0.661 ^t |
| Reticulocyte count ≤7% | 64 (58.18) | 38 (59.38) | 26 (56.52) | - |
| Reticulocyte count >7% | 46 (41.81) | 26 (40.62) | 20 (43.47) | |
| Method of exchange | UV-PV: 114 (98.27) | UV-PV: 65 (97.01) | UV-PV: 49 (100) | - |
| | UA-UV: 1 (0.86) | UA-UV: 1 (1.49) | | |
| | PA-PV: 1 (0.86) | PA-PV: 1 (1.49) | | |

[Table/Fig-1]: Baseline characteristics of study participants (N=116). Values presented as Mean±SD/ n (%)/Median {Inter Quartile Range (IQR)}; ^tIndependent samples t-test; ^cChi-square test; ^mMann-Whitney U test; GA: Gestational age; LSCS: Lower segment caesarean section; VD: Vaginal delivery; DCT: Direct Coombs test; UV: Umbilical vein; UA: Umbilical artery, PA: Peripheral artery; PV: Peripheral vein; The p-value in bold font indicates statistically significant value

There was a statistically significant difference in postexchange bilirubin, the percentage drop in bilirubin, and the rebound bilirubin at six hours between the two groups. However, the duration of phototherapy, duration of admission and discharge bilirubin were similar in both groups. Six patients in group 1 required more than one exchange transfusion. They had Rh isoimmunisation and received an average blood volume of 86.4 mL/kg for the first exchange [Table/Fig-2].

A positive correlation (r-value=0.548, p-value<0.001) was noted between the percentage drop in bilirubin and the volume of blood

| Variables | All subjects (N=116) | Group 1 (n=67) | Group 2 (n=49) | p-value |
|---|----------------------|--------------------|-------------------|---------------------|
| Mean pre-exchange bilirubin (mg/dL) | 22.569±5.24 | 22.493±5.505 | 22.673±4.917 | 0.855 ^t |
| Volume of blood used for exchange (mL) | 353.58±92.89 | 295.63±36.09 | 432.84±88.23 | <0.001 ^t |
| Volume of blood (mL/kg) | 119.90±30.56 | 97.02±13.31 | 151.19±16.29 | <0.001 ^t |
| Duration of exchange (minutes) | 80.07±28.39 | 74.75±28.89 | 87.37±26.26 | 0.017 ^t |
| Postexchange bilirubin | 11.9±3.7 | 13.12±3.85 | 10.26±2.78 | <0.001 ^t |
| Percentage drop in bilirubin | 46.26±13.90 | 40.74±12.81 | 53.81±11.67 | <0.001 ^t |
| Rebound bilirubin at 6 hours (mg/dL) | 12.34±3.71 | 13.15±4.32 | 11.23±2.30 | 0.006 ^t |
| Percentage rise of bilirubin at 6 hours | 6.31±22.08 | 1.23±19.92 | 13.25±23.2 | 0.002 ^t |
| More than 1 exchange | 6 (5.17) | 6 (8.96) | 0 | |
| Duration of phototherapy (hours) | 48 (36-78) | 48 (36-96) | 48 (42-72) | 0.977 ^m |
| Duration of admission (days) | 5 (4-7) | 5 (4-7) 6.090±3.73 | 5 (4-7) 6.55±4.38 | 0.711 ^m |
| Discharge bilirubin (mg/dL) | 8.47±2.32 | 8.38±2.41 | 8.60±2.20 | 0.616 ^t |

[Table/Fig-2]: Comparison of serum bilirubin levels, volume of blood used, duration of exchange, postexchange bilirubin levels and treatment duration in the two studied groups.

Values presented as Mean±SD/ n (%)/ Median (IQR); ^tIndependent samples t-test; ^mMann-Whitney U test

used for exchange transfusion. The positive significant correlation was seen only in group 1 ($r=0.572$, $p\text{-value}<0.001$). No significant correlation was seen in group 2 ($r=0.031$, $p\text{-value}=0.83$). While the rebound rise in bilirubin at six hours had a weak correlation with the volume of blood used for exchange, the other parameters like the total duration of phototherapy and duration of admission had no significant correlation [Table/Fig-3].

The postexchange values of haemoglobin and electrolytes were significantly different from the pre-exchange values, except for haemoglobin and sodium in group 2 patients [Table/Fig-4]. The post-transfusion platelet values were available only for 65 patients,

and among them, 53.8% had thrombocytopenia. No significant difference in complications was seen between the two groups [Table/Fig-5]. Postexchange thrombocytopenia and electrolyte imbalances are well-documented in the literature. None of the patients had complications warranting active management. There was no mortality related to exchange transfusion in the present study.

DISCUSSION

Exchange transfusion is the only available treatment for infants at risk of bilirubin encephalopathy, who are unresponsive to

| Correlation of exchange blood volume with: | Total participants | Group 1 | Group 2 |
|--|-------------------------|--------------------------|------------------------|
| Percentage drop of bilirubin | $r=0.548$; $p<0.001$ | $r=0.572$; $p<0.001$ | $r=0.031$; $p=0.834$ |
| Rebound rise in bilirubin at 6 hours | $r=0.274$; $p=0.003$ | $r=-0.026$; $p=0.84$ | $r=0.182$; $p=0.21$ |
| Duration of phototherapy | $r_s=-0.04$; $p=0.667$ | $r_s=-0.136$; $p=0.274$ | $r_s=0.51$; $p=0.730$ |
| Duration of admission | $r_s=0.033$; 0.725 | $r=0.1$; $p=0.423$ | $r=0.102$; 0.487 |

[Table/Fig-3]: Correlation of exchange blood volume with treatment effects.

r: r-value; p: p-value

| Parameters | | Normal range | Pre-exchange | Postexchange | p-value |
|---------------------|----------------|---------------|--------------|--------------|---------------------|
| Haemoglobin (n=111) | Group 1 (n=64) | 15-24 gm/dL | 14.19±3.20 | 17.69±2.47 | <0.001 ^p |
| | Group 2 (n=47) | | 16.10±2.98 | 15.345±3.70 | 0.330 ^p |
| Sodium (N=116) | Group 1 (n=67) | 133-146 mEq/L | 143.24±5.35 | 141.37±4.41 | <0.001 ^p |
| | Group 2 (n=49) | | 143.10±5.91 | 143.04±4.38 | 0.92 ^p |
| Potassium (N=116) | Group 1 (n=67) | 3.2-6 mEq/L | 4.70±0.72 | 4.06±0.72 | <0.001 ^p |
| | Group 2 (n=49) | | 4.76±0.802 | 3.786±0.595 | <0.001 ^p |
| Calcium (N=116) | Group 1 (n=67) | 7-10.9 mg/dL | 9.33±1.35 | 8.40±1.04 | <0.001 ^p |
| | Group 2 (n=49) | | 9.44±1.14 | 8.82±1.05 | <0.001 ^p |

[Table/Fig-4]: Pre and postexchange laboratory parameters.

^pPaired t-test

| Adverse effects | Affected participants, n (%) | Group 1 (n=67), n (%) | Group 2 (n=49), n (%) | p-value |
|------------------------------------|------------------------------|-----------------------|-----------------------|--------------------|
| Hyponatraemia (<130 mEq/L) (N=116) | 0 | 0 | 0 | - |
| Hypokalaemia (<3.5 mEq/L) (N=116) | 26 (22.4) | 12 (17.91) | 14 (28.57) | 0.174 ^c |
| Hypocalcaemia (<7.5 mg/dL) (N=116) | 21 (18.10) | 16 (23.88) | 5 (10.20) | 0.059 ^c |
| Thrombocytopenia (<1.5 L) (n=65) | 35 (53.8) | 23/41 (56.09) | 12/24 (50) | 0.634 ^c |
| Sepsis (N=116) | 9 (7.76) | 6 (8.95) | 3 (6.12) | 0.723 ^c |

[Table/Fig-5]: Adverse effects related to exchange transfusion.

^cChi-square test

intensive phototherapy. The recommended double volume exchange treatment, as practiced in various parts of the world [12-15], typically results in a reduction of serum bilirubin by 40-60% [13,14,16].

In the current study, the average volume of blood used per patient is around 353.58±92.89 mL, translating to approximately 120 mL/kg, markedly less than current treatment guidelines. The mean drop in observed serum bilirubin was 47.27%. The drop in bilirubin showed a positive correlation with the volume of blood used. Serum bilirubin reduction in group 2 was 53%, consistent with earlier findings. Group 1, which had a significantly smaller exchange volume, also displayed a 40% drop in bilirubin. A recent study from China claims to have achieved a 50% reduction in bilirubin with a single volume exchange [17]. Previous studies have documented a rebound rise of bilirubin at six hours postexchange period to be around 60% [13,18]. In the present study, the six hours postexchange bilirubin had risen in group 1 and 2 to

patients were admitted for a median duration of five days in both groups.

The duration of phototherapy, the length of hospital stay, or the bilirubin levels at discharge were not affected by the low volume exchange, despite the fact that the initial decline in serum bilirubin was 13% lower in group 1. Predischarge bilirubin levels were 8.38 and 8.60 mg/dL in group 1 and group 2, respectively, which were below treatment thresholds.

The appropriate use of phototherapy has contributed to a reduction in the number of exchange transfusions worldwide [21,22]. All patients in the present study underwent double surface phototherapy in the postexchange transfusion period. This may be the reason why, despite the use of a reduced volume of exchange, group 1 patients did not require a prolonged duration of treatment. A comparison of previously published literature with current study is shown in [Table/ Fig-6] [12-17,20,23].

| Author | Place and year of the study | Number of patients | Volume of blood | Mean pre-exchange bilirubin (mg/dL) | Mean post-exchange bilirubin (mg/dL) | Duration of admission (days) | Duration of phototherapy (hours) |
|--------------------------------|-----------------------------|--------------------|-----------------|-------------------------------------|--------------------------------------|------------------------------|----------------------------------|
| Hakan N et al., [12] | Turkey, 2015 | 306 | NA | 25.8±6.6 | NA | NA | NA |
| Bujandric N and Grujic J, [23] | Serbia, 2016 | 398 | 660 mL | NA | NA | NA | NA |
| Kakkar B et al., [14] | India, 2019 | 14 | 422 mL | 16.5±6.5 | 9.2±3.6 | NA | NA |
| Wolf MF et al., [20] | USA, 2020 | 1252 | NA | 20 | 15 | NA | NA |
| Duan L et al., [16] | China, 2021 | 120 | NA | 25.72±5.4 | 13.56±3.15 | 9.28±3.3 | NA |
| Okulu E et al., [15] | Turkey, 2021 | 132 | 160-180 mL/kg | 24.9±9.1 | NA | NA | NA |
| Boskabadi H et al., [13] | Iran, 2022 | 379 | 180 mL/kg | 22.99±4.04 | 12.57±3.83 | NA | NA |
| Xiong Z et al., [17] | China, 2023 | 48 | 80-110 mL/kg | 24.61±3.55 | 11.92±1.50 | 9.14±3.78 | 56.43±21.89 |
| | | 48 | 150-180 mL/kg | 25.37±3.34 | 11.13±1.37 | 9.75±4.05 | 49.40±18.91 |
| Present study | India, 2023 | 67 | 80-≤120 mL/kg | 22.493±5.505 | 13.12±3.85 | 5 | 48(36-96) |
| | | 49 | 120-<160 mL/kg | 22.673±4.917 | 10.26±2.78 | 5 | 48(42-72) |

[Table/Fig-6]: Comparison of the present study with published literature [12-17,20,23].

58.42% and 49.53% of pre-exchange levels, respectively. There were 6 (8.95%) patients in group 1 who required repeat exchange transfusion, indicating that patients who received lower volume exchange must be kept under monitoring to detect further rise in bilirubin.

Many adverse events related to exchange transfusions, including life-threatening ones, have been documented in the literature. Hypocalcaemia and thrombocytopenia in the postexchange period are documented in many studies [13,14,19,20]. It is thought that the volume of exchange, duration and route are major factors affecting the incidence of complications [7,10]. In the present study, although authors observed hypokalaemia, hypocalcaemia, thrombocytopenia and sepsis, there was no statistical difference in the incidence of complications on group-wise analysis. Postexchange thrombocytopenia is a well-known complication of exchange transfusion. The authors observed that repeat examinations after 24 hours usually show a rise in platelets. Electrolyte changes also usually self-correct.

Postexchange transfusion, the patients continued on phototherapy for a median duration of 48 hours in both group 1 and group 2. Documentation regarding the duration of phototherapy that the subjects received in the postexchange phase is scarce in the literature. Many have reported hospital stays ranging from 9-10 days [16,17]. In the current study, the

Limitation(s)

The study is retrospective in nature. The postexchange platelet values of many patients were not available, and there is no control population. The authors were not sure whether they can extrapolate the same results to a push-pull technique of exchange transfusion or to preterm patients.

CONCLUSION(S)

Exchange transfusion with a lower volume of blood, followed by phototherapy, can lead to a clinically acceptable reduction in serum bilirubin. Patients who have received a lower volume exchange must continue to receive phototherapy, and their bilirubin levels should be monitored for any subsequent rise. Proceeding with exchange, even when the blood volume is less than 160 mL/kg, is therefore advantageous for the patient.

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Authors contribution: Krishna Kumar Diwakar conceptualised the paper. Manu Rajan Idicula planned and developed the protocol, completed the ethics application, collected the data and analysed the results. Leela Sudhakaran Kamath and Manu Rajan Idicula edited and

revised the manuscript. All authors were responsible for interpreting the results, drafting and revising the manuscript and its final approval.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Neonatology, Malankara Orthodox Syrian Church Medical College, Ernakulam, Kerala, India.
2. Professor, Department of Neonatology, Malankara Orthodox Syrian Church Medical College, Ernakulam, Kerala, India.
3. Professor, Department of Neonatology, Malankara Orthodox Syrian Church Medical College, Ernakulam, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Manu Rajan Idicula,
Assistant Professor, Department of Neonatology, Malankara Orthodox Syrian Church Medical College, Kolenchery-682311, Ernakulam, Kerala, India.
E-mail: manurq@outlook.com

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