Role of Automated Therapeutic Red Cell Exchange in the Setting of Acute Methemoglobinemia: Our Experience

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Abstract Methemoglobinemia, an altered state of hemoglobin resulting in impaired oxygen delivery to the tissues can be congenital or following exposure/ingestion of various oxidant drugs or toxins. One of the earliest signs of methemoglobinemia is generalized cyanosis not improved on oxygen supplementation and presence of normal PO₂ on acid blood-gas analysis. Here, we report two cases of acquired methemoglobinemia following poisoning and our experience of managing them with automated therapeutic red cell exchange.

Keywords Therapeutic red cell exchange · Methemoglobinemia · Aniline poisoning

Case 1

A 2 year old child with alleged h/o aniline dye ingestion leading to involuntary movements and difficulty in breathing with cyanosis and gasping was immediately rushed to some nearby hospital where he was put on ventilator. Partial manual red cell exchange was tried which lead to hemodynamic instability and patient was referred to us.

On examination, baby's GCS was poor, was cyanosed, dehydrated. BP-86/46, pulse 168/min and oxygen saturation 80% with variable self respiratory rate.

As methemoglobinemia was evident, samples for its estimation were sent to the outsourced lab. Inj methylene blue was being arranged and sample for G6PD estimation

was sent. Seeing the emergency, therapeutic red cell exchange was considered as the best possible and feasible option. Samples for pre procedure work up which included ABO and Rh(D) Typing, Antibody screening, DCT, Viral markers (ECi and NAT) were sent to blood bank. Upon receipt of the request, immediately two units of LDPRBC (irradiated) with a Hct between 60 and 65% were cross-matched. The baby was 15 kg so the blood-priming of the extracorporeal circuit of the cell separator was done. TBV of the baby was estimated to be 1200 ml with Hct 29% and the one volume red-cell mass was calculated (348 ml). An exchange of 1.3 red-cell volume was planned. Procedure was done on automated cell separator on COM-TEC (Fresenius). During this process, 800 ml of TBV was processed. Baby was pre-medicated and pre-procedure Ionised Ca estimated and supplemented to manage the citrate effects. The procedure was over within 40 min and reinfusion was done. The baseline and post procedure vitals are given in the Table 1.

Initial and post-procedure methemoglobin levels were 24 and 16% respectively. Due to cost constraint, next procedure was not done and further management was with Inj methylene blue. Total 3 doses were given and within 3 days, the baby was off ventilator and after 7 days of inpatient treatment was discharged in a good condition.

Case 2

A 21 year old intubated male patient was brought to our emergency room R with c/o restlessness and breathing difficulty following alleged h/o ingestion of some unknown liquid poison at work. He had vomiting but no h/o loss of consciousness and seizures. ABG indicated severe metabolic acidosis and was on controlled mode of ventilator with FiO₂ 100%, on examination bilateral

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Table 1 Baseline and Post procedure vitals for Case 1

Vitals	BP	Pulse	Respiration	SPO ₂ (%)	Met Hb (%)
Pre procedure	91/52	162	32	76	24
Post procedure	116/67	164	32	94	16

chest air entry (+), SpO₂ 82%, peripheral cyanosis (+) and abdomen non-distended. Hemodynamically stable. Blood was chocolate brown in color along with a gap of 10 in between/w SpO₂ on ABG and pulse oximetry, pointing towards methemoglobinemia. MetHb levels were sent for estimation.

Red cell exchange was planned for the patient as the first line treatment. The pre procedure workup was done including ABO and Rh (D) typing, antibody screening, DCT, viral markers (ECi and NAT). The boy was 45 kg with 35% Hct, his TBV as calculated was 3150 ml and his one red-cell volume was 1100 ml. Red cell exchange of 1.2 volumes was planned for which LDPRBC of Hct 60–65% were crossmatched. The total time for the procedure was 45 min and four units of LDPRBC ~ 1300 ml in volume was exchanged. His base line and post procedure vitals were monitored as given in Table 2. Reinfusion was not done.

Initial MetHb levels were 67%. Injection methylene blue was also given one dose. Almost after 5–6 h post-procedure the patient started communicating and cyanosis resolved. In less than 24 h he was extubated making it the shortest stay of a patient on ventilator as per our hospital records. His vitals improved at a drastic rate. The patient was to be under observation for another 48 h but he went LAMA.

Discussion

Methemoglobinemia whether acute or chronic is a condition in which the methemoglobin levels in the blood exceed normal levels (0–2%). Methemoglobin concentrations of 10–20% are tolerated well, but levels above this are often associated with symptoms [1]. In both cases the Met Hb levels were high 24 and 67% respectively resulting in reduced Oxygen delivery to the tissues leading the clinical symptoms. In general MetHb levels above normal result in headache, nausea, vomiting, cyanosis, altered sensorium eventually progressing to drowsiness, coma, and death [2].

The clinical findings suggestive of MetHb are peripheral cyanosis, low oxygen saturation on pulse oximetry, normal partial pressure of oxygen in arterial blood (PaO₂) on ABG and chocolate colored blood. This oxygen “saturation gap” between the SaO₂ and SpO₂ greater than 5%, is diagnostic to the presence of MetHb [3]. Both the cases had these typical features, it was easy to plan management at the earliest. For methemoglobinemia due to drug exposure, traditional first-line therapy consists of an infusion of methylene blue, whose action depends on the availability of reduced NADPH within the red blood cells. As methylene blue availability was not prompt and depending upon the emergency, therapeutic red-cell exchange was considered. Although red-cell exchange is a known indication for drug overdose and poisoning but its role as such in methemoglobinemia is yet to be elucidated. The treatment has potential scope as manual red cell exchange had been tried in a few cases of methemoglobinemia resistant to methylene blue [4, 5].

Major causes of MetHb are either a genetic defect (RBC metabolism or hemoglobin structure) or acquired following exposure to various oxidant drugs or toxins. Commonly implicated drugs are dapsone, local anesthetics, phenacetin, and antimalarials and is associated with hemolytic anemia and Heinz bodies. Occasionally acute intravascular hemolysis can lead to renal failure [6].

Some drugs, such as dapsone, benzocaine, and aniline, produce a rebound methemoglobinemia, in which methemoglobin levels increase 4–12 h after successful methylene blue therapy. Urine output is monitored, and a close eye is kept for evidence of hemolysis and rebound methemoglobinemia [7]. There is evidence in literature which states that while methylene blue in judicious dose reduces the content of methaemoglobin after aniline exposure, it may not eliminate visible cyanosis and repeated injections can markedly aggravate subsequent haemolysis without further lowering methaemoglobin content [8]. This might be the reason why our first case had a prolonged stay of 7 with 3 days ventilator support although his initial MetHb was 24% and post-procedure it was 16%.

Table 2 Baseline and Post-procedure vitals for Case 2

Vitals	BP	Pulse	Respiration	SPO ₂ (%)	Met Hb (%)
Pre procedure	108/86	97	18	86	67
Post procedure	103/70	86	19	93	21

The differential diagnosis of methemoglobinemia includes cyanotic congenital heart disease and sulfhemoglobinemia. The potassium cyanide test can distinguish between methemoglobin and sulfhemoglobin. But as the cause was already known, it was not required.

Methylene blue is an oxidant; and thus can result in hemolysis and, paradoxically, methemoglobinemia in patients with G6PD deficiency. So although it is considered as the first line therapy for drug induced/poisoning related MetHb, a lot of factors need to be considered before using like availability, G6PD status, dose, duration, side effects (rebound methemoglobinemia and hemolysis) [9, 10]. Automated therapeutic red cell exchange which is a much safe, efficacious and promising treatment modality with huge potential can be used in such cases assuring prompt relief following a single or may be a 2 day sitting. Further studies on such cases are required to evaluate the therapy outcomes as a first line modality in terms of efficacy and safety.

Compliance with Ethical Standards

Conflict of interest Anil Khetarpal declares that he has no conflict of interest. Urvershi Kotwal declares that she has no conflict of interest.

Informed Consent Informed consent was obtained from both the patients included in the study before the procedures were done.

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