

Approach to a Rare Entity: Hemolysis due to Dialysis Machine

Nadir Bir Olaya Yaklaşım: Diyaliz Cihazına Bağlı Hemoliz

ABSTRACT

OBJECTIVE: Hemolysis is one of the rare and occasionally fatal complications of hemodialysis. The cause of hemolysis should be found for the prevention of further hemolysis and deaths. The checklist for the cause of hemolysis requires every detail of dialysis process to be reviewed, though clinical experience and the literature are still insufficient to guide medical professionals in solving the problem. The aim of this article was to increase awareness regarding the failure of the current evidence to solve the problem of hemolysis in hemodialysis.

MATERIAL and METHODS: Clinical, procedural and technical data regarding 11 episodes of hemolysis in 9 patients on 5 machines from two hemodialysis centers were investigated. The cause for hemolysis was investigated step by step based on the available evidence and instructions of the respective hemodialysis machines.

RESULTS: Both the frequent and rare causes of hemolysis in hemodialysis such as blood tubing sets, dialysis membranes, needles, water system and machine contamination, chloramines, high temperature dialysis, and hypo-osmolar dialysis were excluded. Technical investigations of the hemodialysis machines by the authorized services were also of no help. Lastly, replacement of the 5 suspected hemodialysis machines resulted in permanent cessation of the hemolysis episodes.

CONCLUSION: The current evidence for the causes of hemolysis in hemodialysis may be insufficient, and replacement of the suspected hemodialysis machines may be the last resort.

KEY WORDS: Dialysis, Hemolysis, Renal dialysis

ÖZ

AMAÇ: Hemoliz, hemodiyaliz nadir görülen ve sıklıkla ölüme yol açabilen bir komplikasyondur. Yeni olguların ve olası ölümlerin yaşanmaması için hemolizin nedeni bulunmalıdır. Klinik bilgi ve tecrübe, sağlık çalışanlarına yol göstermede yetersiz kalıyor olabilmesine rağmen, hemolizin sebebine yönelik diyaliz sırasındaki her detayın incelenmesi gerekmektedir. Makalenin amacı güncel bilgilerin hemolizin sebebini aydınlatmasındaki yetersizliğe dikkat çekmektir.

GEREÇ ve YÖNTEMLER: İki ayrı diyaliz merkezinde toplam 5 cihazda, 9 hastada, 11 kez yaşanan hemolize ait klinik, prosedürel ve teknik bilgiler incelendi. Hemolizin sebebi mevcut güncel bilgi ve kanıtlar ışığında adım adım ilerlenerek aydınlatılmaya çalışıldı.

BULGULAR: Hemolize sebep olabilecek diyaliz seti, diyalizör, iğne, su sistemi, makine kontaminasyonu, kloraminler, yüksek ısılı diyaliz, hipoozmolar diyaliz gibi sık ve nadir nedenler dışlandı. Yetkili diyaliz servisinin teknik incelemesinin de ek katkısı olmadı. Son olarak, şüpheli 5 diyaliz cihazının kullanım dışı bırakılması hemoliz olgularının sonlanmasına yol açtı.

SONUÇ: Güncel kanıtlar hemolizin sebebini aydınlatılmasında yetersiz kalabilir. Şüphelenilen diyaliz cihazlarının kullanılmaması son çare olarak denenebilir.

ANAHTAR SÖZCÜKLER: Diyaliz, Hemoliz, Hemodiyaliz

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INTRODUCTION

Hemolysis during hemodialysis is one of the medical emergencies that can be fatal (1,2). There are many possible causes of hemolysis (1-3). Root cause should be looked for step by step until resolution of the problem. Approach to just one episode of hemolysis is quite different from approaching hemolysis in the epidemic form.

Here we present 12 episodes of hemolysis seen between 20 October 2015 and 23 April 2016 at 2 dialysis centers that were resolved by not using the suspect dialysis machines. In the literature, there are some articles on the various reasons of sporadic cases of hemolysis (4-9). Apart from reviews aiming a theoretical approach to hemolysis (1,2), there are a few articles about clinically experienced hemolysis outbreaks (10-13). The aim of this article was to increase awareness about when and how to suspect hemolysis induced by machine.

MATERIAL and METHODS

The hemolysis episodes that occurred in two hemodialysis centers were promptly investigated by the healthcare professionals and technical team. Consumption products including the fistula needle, blood tubing set, dialysis membrane, and dialysis solution were investigated. Possible causes related to dialysis water system abnormalities, contamination and the dialysis machine itself such as blood pump abnormalities, dialysate composition and temperature errors, and dialysis machine contamination were looked for as well. When no conclusive evidence for hemolysis could be found, a more detailed and stepwise investigation was followed, though the evidence still could not be seen. The results of those investigations are presented herein. All subjects enrolled in this research have given their oral informed consent. Ethical approval or Institutional Review Board approval was not taken because of the retrospective pattern of the report. All procedures were in accord with the declaration of Helsinki. All patients were treated accordingly. Patient names and machine details were kept anonymous for confidentiality.

RESULTS

Patient Characteristics

Hemolysis episodes were seen in an eastern city of Turkey which has a main dialysis unit at the city center and 3 satellite units at other districts. Hemolysis was seen at the main dialysis center and one of the satellite units concomitantly. There were 25 dialysis machines and 90 hemodialysis patients at main the center while the satellite unit had 5 machines and 14 patients.

Hemolysis Episodes

Hemolysis was first seen on 20 October 2015, just 3 weeks after welcoming a new nephrologist to the city. There was no nephrologist in the preceding 8 months. Totally 11 episodes of hemolysis were seen in 9 patients at 5 dialysis machines. The mean age of patients was 50.2 (29-62) years.

Past medical histories were negative for any illness that could cause hemolysis. Five patients were male (55%). Two patients experienced hemolysis twice. Hemolysis episodes were seen twice on machine I, III and V, once on machine II, and four times on machine IV. All machines were produced by the same manufacturer. Production dates were between 2001 and 2008. All machines were continued to be used until 23 April 2016. Hemolysis was diagnosed during (n=5) or after dialysis (n=6). Hemolysis episodes were not grouped at any specific day of the week or session. The main complaint was chest and/or abdominal pain except one case complaining of dark skin. Details about the hemolysis date, location, main complaint and its timing, and machine codes are presented in Table I. Patient names and other machine details were coded for confidentiality.

Stepwise Checklist for Hemolysis

Summary of possible root causes and reasons for their exclusion are presented in Table II.

1. Fistula Needle, Blood Tubing Set, Dialysis Membrane, Blood Pump

After the first two episodes, we thought that the fistula needles might be the possible cause. We started to flush needles with isotonic saline before use to see if there was any sign of stenosis. There seemed to be no problem. The third episode was from a patient with catheter directing us to think other possible etiologies for hemolysis. Single needle dialysis was never used at any of the centers.

Episodes 5 and 6 were diagnosed during dialysis at the satellite center. We had the chance to examine blood tubing sets to see if there was a kink or leakage but all seemed normal. Lot numbers of the blood tubing sets were different during the hemolysis timeframe.

The second 3 episodes' dialysis membranes were different from the first 3 episodes making us consider a reason other than the membranes.

Blood pump rates were convenient for needle size. The diameter of space for blood tubing set at blood pump was appropriate for the diameter of the set.

2. Dialysis Solution, Water System Abnormalities, Water System Contamination

Both centers' solutions were stored appropriately. All of the equipment consumed for dialysis were used before the expiration date.

Acidic solutions' lot numbers were the same for hemolysis episodes 4-6, making them a possible cause. An acidic solution from the same lot number was analyzed at an independent laboratory for any possible production error, microbial contamination and endotoxin level. Electrolytes and endotoxin level were in the expected range. There was no microbial contamination. Basic solutions' lot numbers were different for

Table I: Details about hemolysis date, location, main complaints, timing of main complaint, and machine codes.

Patient Code	Hemolysis episode number	Hemolysis date	Location	Main complaint	Main complaint's timing	Machine Code
Patient A	1	20.10.15	Main center	Chest pain	After dialysis	I
Patient B	2	21.10.15	Main center	Abdominal pain	After dialysis	I
Patient C	3	24.10.15	Main center	Chest pain	After dialysis	II
Patient D	4	31.10.15	Satellite center	Abdominal pain	After dialysis	III
Patient E	5	13.11.15	Satellite center	Chest pain	During dialysis	IV
Patient F	6	14.11.15	Satellite center	Epigastric pain	During dialysis	IV
Patient G	7	18.02.16	Satellite center	Abdominal pain	After dialysis	IV
Patient H	8	19.03.16	Main center	Dark skin	After dialysis	V
Patient J	9	30.03.16	Main center	Fever, chest and abdominal pain	During dialysis	V
Patient D	10	02.04.16	Satellite center	Chest and abdominal pain	During dialysis	III
Patient G	11	23.04.16	Satellite center	Abdominal pain	During dialysis	IV

Table II: Details about possible causes and their exclusion reasons.

Cause	Exclusion reason
Medical conditions causing hemolysis	No specific illness in the medical history. All patients completely recovered
Fistula needle	Hemolysis in a patient with catheter
Kink, leak at blood tubing sets	Normal appearance by inspection
Single needle dialysis	Not used
Dialysis membranes	Products from various companies used
Acidic solution	Analyses were normal
Basic solution	Lot numbers were different
Water system contamination	Analyses were normal
Water system abnormalities	Analyses were normal
Dialysis machine contamination	Analyses were normal
Hypoosmolar dialysis	Machines run experimentally. Results were normal
Overheated dialysate	Calibrations were normal
Excessive ultrafiltration	No weight abnormality during any of the episodes

the hemolysis episodes. Water system test results of the main and satellite centers including total chloride, chloride, fluoride, nitrate, sulphate, aluminum, ammonium, calcium, magnesium, mercury, potassium, sodium, zinc, heavy metals, microbial contamination, bacterial endotoxins were all normal.

3. Dialysis Machine Contamination, Dialysate Composition Abnormalities

Dialysate samples taken from all 5 suspect machines were investigated for microbial contamination and endotoxin levels. No abnormality was found from the tests. Four of the machines were run by technicians for 4 hours. Dialysate samples were taken to determine electrolytes 1 hour apart. All results were in the expected range.

4. Ultraheated Dialysate, Excessive Ultrafiltration

All machines' calibration and alarm backgrounds were checked by technicians regularly many times for the investigation of the root cause. There was nothing to note such as a temperature alarm or conductivity alarm or any signs of unwanted ultrafiltration volumes. Patients' actual weight after dialysis was concordant with the expected post dialysis weight.

We have continued to use these suspect machines until the last hemolysis episode, which was on 23.04.2016. After this time, we decided that all other possible causes for hemolysis have been ruled out and this issue could be related to the machines themselves. Government authorities and official technicians of the manufacturer were informed of the condition again. There was no independent laboratory available for further investigation of the machines. The official technicians have reported several times that all machines were normal. There was nothing more to do other than discarding the suspect machines as an empiric solution even though the manufacturing company was against this. As a result, the suspect machines have not been used. No new hemolysis episode has been seen so far.

Diagnosis, Treatment, and Complications

Hemolysis was suspected by clinical grounds first. Cherry red blood was not seen in any of the episodes. The diagnosis was verified by laboratory parameters. The serum color was concordant with hemolysis at every episode. Serum potassium levels were not increased to lethal levels in any of the episodes. The most striking laboratory abnormality was increased lactate dehydrogenase level and increased indirect bilirubin levels. The direct Coomb's test was negative in all episodes except episodes 1, 2 and 7 where it was unknown. Haptoglobin and reticulocyte counts were not available at our hospital. Dialysis was stopped if we suspected hemolysis during dialysis and the blood was not returned to the patient.

Patient H and patient G at episode 11 had pancreatitis resolving with conservative treatment. Patient J had myocardial infarction treated medically. Patients at episodes 3, 8, 9, 10 had erythrocyte replacement. None of the patients had died due to hemolysis. Patients were hospitalized after all episodes except the first 3 ones once hemolysis was diagnosed. They were not discharged until resolution of complaints and normalization of the lactate dehydrogenase level.

DISCUSSION

We have experienced 11 episodes of hemolysis which ceased by not using the suspect machines. Fortunately no patients have died because of hemolysis. We have tried to enlighten the cause of the hemolysis in a stepwise approach. Since the total time length was approximately 6 months, we tried to find root cause after every episode.

Some medical conditions such as autoimmune diseases including systemic lupus erythematosus, scleroderma, malignant

hypertension, microangiopathic hemolytic anemia secondary to malignancies, sickle cell disease, glucose 6 phosphatase deficiency, mechanical valves and medications (e.g., aspirin, penicillin, hydralazine) can cause hemolysis (1,2). Even though we could not measure the glucose 6 phosphatase enzyme level, our patients did not have any of the illnesses and they did not use any of the medications predisposing to hemolysis. Their lactate dehydrogenase levels returned to normal after resolution of hemolysis showing that an underlying hemolytic process was not present.

Fistula needles were excluded as a cause because there were episodes in patients with dialysis catheters. The centers had never used single needle dialysis in which the hemolysis probability is increased due to higher shear stress and/or a malpositioned needle (2).

Blood tubing sets' lot numbers varied between the episodes, making this possibility unlikely. There is a report on hemolysis secondary to faulty blood tubing sets (10). Thirty case patients were dialyzed at 29 different machines in that report. Our 11 cases were aggregated to only 5 machines. The hemolytic process seen only with some of the machines, directing us to consider the problem was related to these machines, not the water system or consumption products. In addition, hemolysis because of faulty blood tubing sets is expected to occur in the first 2 hours of dialysis but this was not the case in our episodes (2). Arterial prepump and venous postpump pressures were unfortunately not recorded. Even though we achieved to stop hemolysis by another intervention and this excludes blood tubing sets as a cause, it would be more convenient if the pressures were known.

Having unintentionally used two different companies' dialysis membranes in the episodes made it clear that the root cause was not the membranes although this risk is negligible with modern dialysis membranes (2).

Acidic lot numbers of some episodes made us consider whether this was the cause. This was ruled out by examination of acidic solutions even though we were aware that probability of contamination was less for acidic solutions than basic solutions because of the nature of their content. Suspect lot numbers were not used again anyway but it could not prevent further hemolysis episodes.

Chloramines may cause hemolysis outbreaks at dialysis centers as detected by decreased hemoglobin or resistance to erythropoietin stimulating agents as de Oliveira et al reported 8 years ago (14). Our water system test results were normal excluding etiologies such as contamination, chloramines and other metals. Our cases were dispersed to a period of 6 months and limited to some machines. This is different than what we expect from an outbreak because of chloramines as it should not be limited to some machines. Moreover, test results failed to show chloramine toxicity. In addition, water system samples and dialysate samples taken from all of the suspect machines showed neither microbial contamination nor increased endotoxin levels.

Hypoosmolar dialysis is another cause of hemolysis (15). Conductivity alarms were all active in all machines and they were working properly according to the technicians' report. Perdergrast et al reported 4 cases of hemolysis because of dialysis by "distilled water" in which serum sodium has decreased on average 22 mmol/L (16). We have run machines for 4 hours and taken samples hourly to see whether there could be an electrolyte abnormality. All results were in the expected range. Moreover, electrolytes were checked soon after the suspicion of hemolysis. Sodium levels were as expected, excluding hypoosmolar dialysis as a possible etiology.

Higher temperatures over 42°C may cause hemolysis because of protein denaturation and thermal red cell injury (2,17). This probability is decreased by temperature alarms on dialysis machines. In our cases, machine calibrations seemed normal during the hemolysis period. They were checked many times by the manufacturer's technicians.

Excessive ultrafiltration is another cause of hemolysis (4). Kes et al reported two patients with hemolysis in the first hour of hemodialysis. They had decreased blood pressure. The timing of hemolysis is different in our cases. They did not have decreased blood pressure during the hemolytic session. In addition, our patients' post dialysis weights were as expected, making unintentional ultrafiltration volumes unlikely as a cause.

The diagnosis of hemolysis was suspected clinically and proven by laboratory values. Although we were sure of the diagnosis of hemolysis, some laboratory parameters including reticulocyte count and haptoglobin level were lacking because they were not available at our hospital. Cherry red blood was not seen at any of the episodes which is not sine qua non. Symptoms of hemolysis were chest and/or abdominal pain most of the time like other reported cases (10,18). Timing of complaints was towards the end of the session or after it. Some patients presented to the hospital after dialysis and did not mention any problem during dialysis. When these patients were questioned, it was seen that the complaint at the time of presentation was present towards the end of dialysis but they did not mention this. They thought that if they mentioned the problem, dialysis would be stopped and they would be sent to the emergency department which seemed unpleasant to them.

Experiencing hemolysis episodes 11 times was unpleasant both for the patients and medical professionals. Two patients at the satellite center had two episodes. Discarding machines earlier or closing the two dialysis centers for investigation can be discussed as well. We do not have a national/local guideline or regulatory paper for approach to hemolysis so decisions and investigations were done individually. Stopping dialysis at two centers was practically impossible because there was no alternate center nearby. One other reason to continue using machines was repeated reassurance from official technicians about the machine's normal functionality. However, our doubt about the

machines gradually increased. There was no remaining probable reason left other than the machine. As a result, we finally stopped using them.

Hemolysis is accepted as an important complication of dialysis. Searching and finding the cause of hemolysis episodes is not easy. There are only a few articles that provide guidance (1,2). There is a local guideline for management and investigation of hemolysis (3). When we viewed this checklist, we can say that we have tried to do our best to determine the root cause of hemolysis.

This report has some drawbacks. The main reason for hemolysis was the machine but we could not define what the problem was exactly. Machines as root cause of hemolysis are generally placed at the end of the causes of hemolysis list. The cause is listed just as "machine" without giving any more details. It is a vague term and it seems difficult to prove machines as the etiologic agent not only for us but also for other nephrologists. A nephrologist can only reach the end of list by excluding other reasons of hemolysis but cannot prove the problem inside the machine without professional technical help. In other words, obtaining details about the possible reasons of the hemolysis machine's inner mechanisms necessitates an independent investigational laboratory or help from the producer itself. Both of them were lacking in our case unfortunately. Proving the root cause as the machine is like fighting against a dragon at the last and hardest step of an arcade game. You may not hit the dragon without help but can bypass it anyway. As a result, we have not used the machines empirically when trying to define the root cause by bypassing it. Cessation of hemolysis has shown that the right intervention was done. It was the last step that must be taken at such a helpless and dangerous condition. It was safe enough to protect patients from further hemolysis risk. There was no further hemolysis episode until May 2018. We think this result can be accepted as evidence and can be useful as a practical guide in similar conditions.

To the best of our knowledge, an article about hemolysis secondary to machines is not present. Hemolysis more than several times focusing on a machine or a group of machines without any identifiable cause should raise suspicion about hemodialysis machines. Hemodialysis is a prevalent treatment worldwide but investigation of machines further in the case of hemolysis may not be possible in many countries. Nephrologists should not hesitate about discarding suspect machines after ruling out all other reasons.

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