

Anaphylactic reactions to methylprednisolone and gelofusine™ during liver transplant: lesson learnt

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Introduction

Anaphylactic reactions are the most feared and unexpected occurrences which may occur even in absence of history of allergic predisposition. It may be difficult to diagnose an anaphylactic reaction during a surgery like liver transplant which is associated with wide hemodynamic changes. Diagnosis is also made difficult by anaesthesia which modifies the clinical presentation and surgical drapes that may hide the dermal signs of anaphylaxis. In absence of bed side laboratory tests to confirm or refute anaphylaxis during surgery under anaesthesia, it is necessary to maintain high index of suspicion to such possibility and is the key to timely diagnosis and management. We describe here, two anaphylactic reactions during two separate liver transplant surgeries, suspected on the basis of proximate cause analysis, their management and the lessons learnt.

Case 1

A 47 year old male was posted for living donor liver transplant surgery (LDLT) for ethanol related chronic liver failure. His child score was 13, Model for End stage Liver Disease (MELD) score was 23 and MELD sodium score was 26. Creatinine clearance was 69ml/min and there was evidence of moderate intrapulmonary right to left shunt upon cardiology evaluation. Patient had no history of any drug allergy or any other atopic predisposition and had no other co-morbid condition. Donor was American society of Anesthesiology (ASA) class 1 and had no history suggestive of atopic predisposition either. Anaesthesia was standard with induction of anaesthesia using propofol and fentanyl with atracurium for neuromuscular blockade. Anaesthesia was maintained with isoflurane in oxygen and air. Noradrenaline and vasopressin infusions were titrated to maintain perfusion pressures. Antibiotics were repeated after every 3 half-lives and ascites fluid was replaced with Human Albumin. No blood products were transfused in the dissection and anhepatic phase. During anhepatic phase, Gelofusine™, a modified gelatin based plasma substitute was given intravenously. No sooner had the 500 ml of the container was finished, sudden severe vasoplegia ensued with systemic vascular resistance (SVR) falling to around 250 dynes. sec.cm^{-5} . Surgical field that was absolutely dry with no bleeding was immediately filled with saline incase air embolism was the reason. The arterial blood gas (ABG) analysis done an hour before the event was normal with no metabolic or respiratory acidosis. The vasoplegia was nonresponsive to incremental doses of noradrenaline and vasopressin, and also to boluses of phenylephrine and to rapid fluid administration. External cardiac massage was started. Transoesophageal echocardiography was done. Biventricular systolic function was normal, with no evidence of pulmonary embolism. Soon the airway pressures begin to increase and it became increasingly difficult to mechanically ventilate the lungs. Severe respiratory acidosis was seen on ABG. Allergic reaction was then suspected and because of temporal association, Gelofusine was incriminated. Injection hydrocortisone 200mg. and injection Pheniramine 45mg.

were given along with three boluses of epinephrine of 100microgram each. Blood pressure and SVR responded immediately. The episode lasted 26 minutes. Airway pressures normalized in another hour and the respiratory acidosis resolved over next 2 hours. Rest of the surgery and hospital stay was uneventful and patient made complete recovery. Serum immunoglobulin, IgE levels sent after the event, was raised, confirming an allergic reaction. Patient denied permission for skin allergy test while more sophisticated confirmatory Basophil activation test is not available.

Case 2

A 44 year old patient, of alcohol induced chronic liver disease with portal hypertension, decompensated with ascites was posted for LDLT. His MELD score was 23 and MELD sodium score was 26. Creatinine clearance was 122ml/min and cardiology workup documented minimal intrapulmonary right to left shunt. Neither the patient nor the donor had history of any drug allergy or any other atopic predisposition. Co-morbid conditions of the patient included non-insulin dependent, diet controlled diabetes mellitus of less than 2 year duration. Anaesthesia was standard and invasive monitoring was established as per the institute's protocol. Native liver was dissected. No blood products were transfused during dissection and anhepatic phase. Porto-caval shunt was created to prevent intestinal edema while the liver graft was awaited from the donor. Portocaval shunt was undone upon receipt of the liver graft to implant the new liver. Infusion of Injection methylprednisolone sodium succinate (MPSS) 1gm. in 100ml. normal saline (10mg/ml.) was gradually started in anticipation of reperfusion of new liver in another hour. ABG was done as per protocol which was unremarkable.

Approximately 15ml of MPSS solution was infused when patient developed sudden and severe hypotension with equally sudden decline in the end tidal carbon di-oxide (ETCO_2) which was unresponsive to stepping up of noradrenaline and vasopressin infusion, rapid fluid infusion and to Phenylephrine boluses. Due to decline in ETCO_2 , air embolism was suspected. Surgical field was flooded with saline and

Trans-esophageal echocardiography (TEE) was done which showed no evidence of air embolism. Soon airway pressures increased and it became increasingly difficult to ventilate the lungs. ABG revealed severe respiratory acidosis. External cardiac massage was started. External cardiac massage was not very effective, therefore it was decided to cut open the diaphragm and internal cardiac massage was started. Due to temporal association, anaphylactic reaction to methylprednisolone was suspected and it was stopped. Injection hydrocortisone 200mg. with injection Pheniramine 45mg. were given along with two boluses of epinephrine of 100 microgram each. Within minutes, the blood pressure recovered and inotropes and vasopressors were tapered to minimal. Airway pressures began to settle down. The total duration of the episode was 25 minutes. Hypercarbia and respiratory acidosis resolved over another 2 hours. Subsequent surgery and hospital stay was uneventful. This Patient also denied permission

for skin allergy test while more sophisticated confirmatory Basophil activation test is still not available.

Discussion

Anaphylaxis is defined as “a serious, life-threatening generalized or systemic hypersensitivity reaction” and as “a serious allergic reaction that is rapid in onset and might cause death”.¹ A clinical diagnosis of anaphylaxis is made when there is “Multiple-organ hypersensitivity characterized by the presence of significant gastrointestinal, respiratory, or cardiovascular involvement, in addition to skin features. Skin features may be transient, subtle, and therefore easily missed, in which case anaphylaxis may still be diagnosed if there is an otherwise typical presentation, especially where this follows exposure to a known precipitant.” World Allergy organization has set clinical criteria for diagnosis of anaphylaxis (Table 1).² Both of our patients satisfied the criteria laid for the diagnosis.

Table 1 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula) and at Least One of the following: A) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) B) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia _collapse_, syncope, incontinence) OR
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours) A) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula) B) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) C) Reduced blood pressure or associated symptoms (eg, hypotonia _collapse_, syncope, incontinence) D) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours) A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure B) Adults: systolic blood pressure of less than 90mm Hg or greater than 30% decrease from that person's baseline

Anaphylactic reaction is labeled as severe in presence of severe hypotension or circulatory collapse.³ Clinical signs in our patients confirmed to the diagnostic criteria and in view of the observed circulatory collapse had severe anaphylactic reaction. The key to diagnosis of anaphylaxis involves pattern recognition with sudden onset of characteristic symptoms and signs within minutes to hours after exposure to a known or potential trigger, which may be followed by rapid progression of symptoms and signs over hours.^{2,4} This recognition of pattern and temporal association becomes important especially during anaesthesia for surgery due to use of multiple drugs that can potentially be the cause. In the peri-operative period, anaphylactic reaction can occur from drugs, including antibiotics, anaesthetic agents, intravenous fluid fluids, and blood products.⁵⁻⁷ Neither of our patients received any blood product till the time the anaphylactic reaction occurred.

In view of temporal association with the circulatory compromise, we implicated methylprednisolone and Gelofusine as the most likely causes which were then stopped and the treatment was given. While repeat exposure to the implicated agents was avoided, anaesthetic agents were continued without recurrence of the anaphylactic reaction and the treatment led to the resolution of the anaphylactic reaction. Methylprednisolone is routinely given as part of immunosuppression during liver transplant surgery and so is Gelofusine™ as a colloid and plasma expander for maintenance of intravascular fluid volume and to curtail the excessive use of crystalloids. While methylprednisolone is infused slowly and is timed to finish immediately before reperfusion, Gelofusine™ is often given rapidly. Anaphylactic reaction to methylprednisolone is reported in literature as individual case reports. Sams & smith⁸ first described

steroid-induced anaphylactic reactions and contact hypersensitivity. While allergy to topical steroid preparations is relatively known, Type 1 (immediate) allergic reactions to systemic glucocorticoids is rare (0.3%).^{9,10} Hydrocortisone, prednisone, and methylprednisolone are commonly reported as cause for anaphylaxis-like reactions. Allergic reactions to systemic corticosteroids are known to be immunoglobulin E (IgE) mediated.¹¹ Blood sample of our patients, sent soon after the suspected anaphylactic reaction revealed raised immunoglobulin E levels, 271 International Units/ml in first and 232 IU/ml in the second patient (Reference range <100 IU/ml) and therefore the observed anaphylactic reaction were also IgE mediated.

Anaphylaxis due to Gelofusine and other plasma expanders is reported in literature with an estimated incidence of 0.066%-0.146%.¹²⁻¹⁴ However, severe anaphylaxis with Gelofusine is rare (0.007%), and these reactions are also type I, IgE-mediated. There may be production of antibodies through prior sensitization, although in many cases antibodies may even occur without any previous documented exposure.^{15,16} IgE levels of our patient were raised after the event in absence of prior exposure to Gelofusine. In solid organ transplant, history of allergic reaction in the organ donor has also been implicated as cause of allergic reaction subsequently in the organ recipient¹⁷ and must be borne in mind should an allergic reaction occurs in an organ transplant recipient. Such consideration however is not applicable in our cases.

Often, due to polypharmacy during anaesthesia it is difficult to elucidate a single agent causing the anaphylactic response. However temporal association of the anaphylactic reaction and its resolution following removal of the implicated drug and non-recurrence despite continuation of the other drugs during the remainder of the surgery

strongly confirms the causative relationship. New sophisticated laboratory tests are described for confirmation of the allergic reaction. Serum tryptase level peak 1 h after an allergic reaction, and can remain elevated for several days. However, this test is not specific in recognizing the causative agent. Another in vitro test is Basophil activation test (BAT). The BAT, for gelofusine allergy has a sensitivity of 100% and a specificity of 87.5%. However in view of the non-availability of these tests and denial of the consent for intradermal allergy test the temporal association and raised IgE tests were relied upon to establish the diagnosis.

These two anaphylactic reactions occurred before the Neohepatic phase and were therefore identified and managed. Had they occurred during reperfusion, which is always a possibility as Methylprednisolone as well as Gelofusine is commonly used during reperfusion, it would have been difficult to differentiate from post reperfusion syndrome which is defined as a decrease in systemic blood pressure during the first 5 minutes of liver reperfusion and management require inotropes and or vasopressor.¹⁸ Specific treatment to treat anaphylactic reaction therefore could have been delayed. Though we implicated the formulations, Methylprednisolone and Gelofusine, as the cause for the observed anaphylactic reactions, the diagnosis is only circumstantial and any other drug used could instead have been the cause. However in view of the difficulty that such an episode may present in diagnosis and differentiating from reperfusion syndrome, anaesthesia protocol at our institute was modified to time the methylprednisolone infusion such that it is finished at least 30 minutes before the intended reperfusion and to use only crystalloid and no synthetic colloid plasma expanders for the management of hypotension during the reperfusion period. Repeat dose of antibiotic for the same reason is also now rescheduled if need be, to avoid timing around reperfusion. The patients discussed here consented to submission of case reports for scientific publication.

Conclusion

Anaphylactic reaction to commonly used formulations during any surgical procedure, including liver transplant surgery, should therefore be considered during management of clinical presentation similar to those discussed in this report.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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