Peer Review File

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Reviewer A

Summary: The authors share an important case report of hypovolemic shock secondary to rhabdomyolysis after prolonged DIEP flap breast reconstruction secondary to flap congestion. The case report is detailed and well-written.

1. The reason why this patient experienced rhabdomyolysis is that the case lasted 18 hours. An elective operative case should not last longer than 6 hours. The authors should emphasize their mistake of continuing the surgery after this time period and discuss what steps will be taken in the future to limit operative time to prevent this from happening again.

Reply 1: Thank you for your insightful comment. This case involves a patient that performed immediate breast reconstruction after skin sparing mastectomy. 18 hours is the total time ranging from when the patient entered and exited the operating room, and after the patient entered the operating room, we prepared to give anesthesia and general anesthesia was performed and preoperative drape was applied and the breast surgeon performed SSM and SLNB. All of these processes took 3 hours~ 4 hours and we began the surgery afterward. Moreover, we searched for IMA and vein in the breast area and exposed it to perform DIEP and implement anastomosis but the arterial inflow was within 20~30 minutes so we repeated the process of stopping about 3 times and found out that the blood supply did not improve. Moreover, we changed the plan to pedicled TRAM after 3 hours passed for the ischemic time of the DIEP flap to conduct the breast reconstruction so we consider that the total operative time was 18 hours. Additionally, in the two or three reanastomosis, there was an influence on the quality of the vessel but we consider that the operator's lack of experience is a part of the reason. Accordingly, we wanted to emphasize that we want to base on this case to make a prompt and appropriate selection of the operation plan and make decisions in the future.

We ask for your positive consideration. Thank you.

2. This case report should not be reviewed as a "successful outcome in a patient with postoperative rhabdomyolysis resulting from prolonged breast reconstruction using an abdominal flap." Postoperatively, the patient experienced hypovolemic shock, and metabolic acidosis requiring CRRT, and nearly died. In prolonging the surgery for 18 hours to save the flap, the authors subjected the patient to unnecessary risk and potential for complications. The authors should outline specifically what steps should be taken in the future to avoid prolonged operative time and the risk of rhabdomyolysis.

Reply 1: Thank you for your delicate comments.

After the surgery, our patient experienced hypovolemic shock and metabolic acidosis and was exposed to a dangerous condition, so we reminded ourselves many times that we should be careful about the recovery process after CRRT and to be successful in the operation indication and

selection, decision. Until now, we performed numerous reconstructions in the breast and other parts by using a free flap but there was no case of an outbreak in rhabdomyolysis like this case. The operative time was prolonged and delayed compared to previous surgeries so we were incautious about the risk of rhabdomyolysis and we consider this as a part of the reason so we have deep regrets as surgeons. In the case of future surgeries, we will avoid prolonged operative time and we will thoroughly check the input/output of the volume in intraop and postop to reduce the risk of rhabdomyolysis. Also, the most important condition is to ensure that we do not fail the most vital procedure, which is the micro-anastomosis, and if it is considered difficult to recover the condition of the flap, we should immediately go with the 2nd choice plan as the decision to prevent the outbreak of the complications.

Reviewer B

The authors present a case of rhabdomyolysis after a prolonged DIEP/TRAM Flap reconstruction. Although this is an interesting case, similar studies have already been published in the literature, as shown in references 15 and 16. For this reason, it lacks an original idea and contribution to the field. Not an original idea. Two studies have already been published with proper strategies to mitigate this type of complications. <u>https://link.springer.com/chapter/10.1007/978-3-319-18726-6_137</u>

Reply 1: Thank you for your comments.

In both references 15 and 16, they are similar since they are rhabdomyolysis cases that occurred in relation to the breast reconstruction surgery, but both studies are cases where a pressure sore or compartment syndrome occurred in the ankle area. In this case report, they could be similar but it is a case where pressure sore occurred in the coccyx and the coccyx part is usually forced, so it is a part where sanctions like a pillowy foam or sponge are imposed on the surgery bed to take caution. Even in this case, there was support with enough foam + sponge, but it occurred due to prolonged surgery and after the surgery, there were delirium symptoms and nothing was wrong with the patient Sx disclosed externally but after the delayed occurrence of the rhabdomyolysis, it was considered as a rather unique case so this case report was deliberated. Reference 15 and 16 were important references to decide the treatment of this case, and after this case, the importance of case reports was perceived at the same time, so we began to prepare this case report, which is a rare case, so that we can share with many breast reconstructive surgeons.

Reviewer C

Dear authors, this is an interesting case and thankfully the patient did well postoperatively, however, there are a few comments:

1) 18 hours for a unilateral DIEP flap is too long, even in light of intraoperative congestion/decision to perform a pedicled TRAM, a large number of surgeons would say that the operation's risk-benefit is unfavorable. If operative times close to this are routine, perhaps implant-based reconstruction could be better options.

Reply 1: Thank you for your consideration.

Until now, we implemented many reconstruction surgeries and observed the prognosis and whenever there was intraoperative congestion, we did not solve it immediately and if it occurs, there were occasional cases of emergency re-operation shortly. This critically troubled the general condition of the patient. As a result, we considered that it is better to terminate the surgery if we conduct an intraoperative flap check and confirm that it is fair. However, 18 hours includes the entire operative time, from when the patient entered the operative room and until when the patient left the operative room. This was a case of breast cancer so skin sparing mastectomy, SLNB was performed first and reconstruction started after completing the confirmation so we cannot say that we only performed the breast reconstruction for a total of 18 hours. In addition, we did not expect that the operative time would be extended for this long. From now on, we will check the ischemic time better and if fair blood supply is not confirmed in the flap at around 3 hours after the operative time began, we will make a prompt decision to turn to the 2nd choice plan and after the surgery, we will do input and output (I/O) check and closely observe sore or injuries in another area other than the surgical area. Before the surgery, we suggested the patient consider breast reconstruction using a breast implant but the patient strongly preferred autologous breast reconstruction over a breast implant and breast reconstruction using an abdominal based flap more than the LD flap so we could not consider other options. But as surgeon doctors, instead of solely following the patient's opinions, we will try to bring low complications and provide good outcomes.

2) There is no mention of intraoperative volume replacement during this case. One of the causes of clinically relevant rhabdomyolysis is insufficient volume resuscitation, so to look at the anesthesia and postop record to see urine output and how much and what type of fluid the patient received would be important in order to evaluate strategies to avoid this problem.

Reply 1: Thank you for your delicate comment.

As explained in the Discussion (page 12, lines 6-14) of the article, the patient's condition monitoring was conducted by an attending anesthesiologist during the surgery, but there were no signs or events of hypovolemia or hypotension. Accordingly, a standard dose was used for all the agents. After the surgery, ambulation was possible so foley was removed and a urine output check was not conducted, and the patient that received the surgery had normal saline (IV, 40ml/hr) of fluid so the protocol was the same as other patients. In addition, although the conversation was not alert due to delirium, we did not consider the risks of injuries because it was not the body part concerned with the surgery and there was a problem of not confirming the pressure sore from the beginning. Moreover, we did not question the occurrence of rhabdomyolysis from the prolonged operation and did not observe the patient's symptoms and we consider this as a crucial limitation and we wrote the report to make sure that this case does not happen again. We wrote this report to look back on our mistakes, analyze and verify the reason, and share the information with all the reconstructive surgeons. Once again, thank you for reviewing the report.

3) we routinely use a large sacral silicone/foam dressing over the sacrum in addition to the bed with foam

Reply 1: Thank you for your delicate comment.

Even in this case, an additional sponge that with about $10\sim12$ cm thickness was placed on the operating table that is already designed with thick foam. In most surgeries, it is set up this way to prevent the occurrence of pressure sore.

Despite this measure, rhabdomyolysis occurred from pressure sore in this case so 50x30x2cm size foam dressing is added as a routine in the sacral section in the operating room to prevent this case from happening. As explained in the figure and explanation in the report, the biggest mistake was delaying the long time operation for too long while maintaining the position that burdened the weight of the whole body only on the sacrum part. After this case, it is a basic condition to make the operating table comfy and soft if there is a possibility of long time operation and we are also considering the position of the patient while we conduct the surgery. Once again, thank you for your helpful comment.

4) Line 355. Pressure sores were observed at the sites of vessel anastomosis on both buttocks following 356 prolonged surgery (POD 3).

Vessel anastomosis doesn't make sense in this sentence

Reply 1: Thank you for your great comment. We agreed that it's not appropriate description. Thus we remove 'at the sites of vessel anastomosis' Changes in the text : page 19, line 1-2. Remove 'at the sites of vessel anastomosis'.

5) there are minor English corrections that should be made (grammar - i.e., verbal tenses etc)

Reply 1: Thank you for your comment.

In the text, there were expressions that seemed to cause an awkward flow in the context and grammatically incorrect expressions, so we have corrected it with English corrections. Thank you. We confirmed a grammatical error in Changes in the text: Page 10, lines 10-11, 'attention to postoperative rhabdomyolysis was delayed' so we revised it to 'postoperative rhabdomyolysis was not immediately suspected.'

We considered that we should clearly express which level Page 10, lines 18-19, 'which was more representative of the actual level' is specifically referring to, so we revised it to the following phrase 'which was a more accurate reflection of the patient's BUN level.'

We revised Page 11, line 10, 'Prior to out patient' more naturally to the following phrase, 'Prior to this case.'

We revised Page 11, line 12, 'while providing ICU care' into 'during our ICU care of the patient' and added more description about the subject under ICU care.

We confirmed grammatical error in Page 11, line 14, 'allowing to localize the site of rhabdomyolysis' so we revised it to 'which allowed us to localize the site of rhabdomyolysis.'

Page 11, line 21-22, 'We believe this positioning was the root cause of the rhabdomyolysis in the present patient.' We revised the expression to make it more smooth like the following. 'We hypothesize that this positioning was the root cause of the rhabdomyolysis in this patient.'

We revised the following into a more objective expression, Page 11, line 23, 'Based on these results, we believe it is essential to identify the patient's risk factors for rhabdomyolysis.'

'Based on these results, our study shows that it is essential to identify the patient's risk factors for rhabdomyolysis'

Page 12, line 8-10, 'Although brain hypoxia was confirmed using a cerebral oximeter, the patient exhibited normal oxygen saturation in the blood flowing into the brain tissues and normal cerebral perfusion.'

The expression of the sentence was not smooth, so we restructured it to make it a more natural sentence, 'Despite confirming brain hypoxia using a cerebral oximeter, the patient's cerebral perfusion and oxygen saturation levels remained normal.'

We confirmed grammatical error in Page 13, line 4, 'Making the current report the first to share information related to patient conditions and treatment progress in such cases' so we revised it as follows. 'This makes the current report the first to share information related to patient conditions and treatment progress in such cases.'

Page 13, line 10-13, 'A position change or placement of a sufficient layer of padding on the operating table to distribute pressure points and prevent ischemic injuries to large muscles must be considered.' The sentence was unnatural grammatically, so we revised it to the following sentence. 'Consideration should be given to changing the patient's position or placing a sufficient layer of padding on the operating table to distribute pressure points and prevent ischemic injuries to large muscles'

We discovered grammatical error in Page 19, line 7, so we revised it as follows. 'Focal debridement for the necrotic tissue was performed and the wound has almost healed after 3 months (POM 3)'

Reviewer D

The article in its current form needs major revisions, I have listed some of them below. My main issue with the case is the cause of the rhabdomyolytis (prolonged buttock pressure periand post operative) and how little is spend on the reflection by the authors.

Comments on article:

• In the abstract it was reported twice "the expected surgical time was exceeded" (line 51 and 56).

Reply 1: Thank you for your comment. In the following text, 'the expected surgical time was exceeded,' the same phrase was used twice so we deleted one of the phrase and combined it into a sentence. Thank you.

Changes in the text : Page 3, line 11-13, 'The surgery exceeded the estimated time because, after anastomosis, severe congestion was observed in the flap and because of the need to perform reanastomosis and the reconstruction of the internal mammary vein twice.'

• The conclusion is incorrect, the occurrence of the rhabdomyolysis has got nothing to do with patient risk factors but all with surgeon/ set up/ anaesthetics team/ post operative management. (line 64-68)

Reply 1: Thank you for your delicate comment. The text mentioned information related to identifying the patient's risk factors, preventing ischemic injury, and reducing complication risks like hypovolemic shock. Preventing the ischemic injury and being prepared for possible rhabdomyolysis means the surgeon to cut down on the operative time as much as possible and prepares during the operative setup to prevent any ischemic injury. In addition, it was intended for the anesthetics team to manage the patients' general condition to lower complication risks like hypovolemic shock and for the surgery team to closely manage the patients with care after the surgery.

• Highlight box – the case cannot be described as a successful outcome, it is a catastrophe for both the patient and department. I am still conflicted on how relevant this information is as I feel like this should have never been able to occur

Reply 1: Thank you for your thoughtful comment. We used the term 'successful' because the patient recovered, but we will change the "successful outcome" into a" rare case". Thank you. Changes in the text: Page 4, highlight box

• Line 106, pre-op renal function would be relevant to add in.

Reply 1: Thank you for your great comment. We added the pre-op renal function on the manuscript. We added the following result,

Changes in the text: Page 6, lines 11-12, 'blood urea nitrogen [BUN] 12.4 mg/dL, serum creatinine [Cr] 0.62 mg/dL' LAB.

• Line 110, DIEP should be written out and the abbreviation between brackets

Reply 1: Thank you for your delicate comment. We add 'deep inferior epigastric artery perforator flap' for the abbreviation DIEP.

Changes in the text: Page 6, line 14-15, 'a free deep inferior epigastric artery perforator(DIEP)

• Figure 1 does not show a position of 30 – 45 degrees

• Line 116, needs rewriting – gives the impression buttock weight loading was the aim of positioning.

Reply 1: Thank you for your consideration.

We agree to change the description related to buttock weight loading and aim of positioning. Thus we modified in the manuscript. Thank you.

Changes in the text: Page 6, line 20-21, 'To optimize weight loading on the buttocks, the patient's upper body was raised by 30° - 45° prior to starting the procedure.'

• Line 119, please explain - don't understand why a insufficiently ligated vein would cause severe congestion

Reply 1: Thank you for your comment

Insufficiently ligated vein can cause resistance and backflow of blood flow, resulting in congestion when the blood flow entering the flap through the artery cannot exit the flap and stagnates within it.

• Line 157, please explain - patient developed ischemia. Do you mean shock?

Reply 1: Thank you for your delicate comment.

'The patient developed ischemia' means whole series of processes of ischemic condition and it lead to sudden shock on POD 3. Therefore, we added additional description in manuscript. Thank you. Changes in the text: Page 8, line 14, 'The patient developed ischemia which lead to shock on POD 3'

• Line 162 – 168, sentence makes little sense and needs to be re-written.

Reply 1: Thank you for your consideration.

We agree to the comment and rewrite the sentence. Thank you.

Changes in the text: Page 8, line 19-23, 'We suspected a release of muscle enzymes from the site of the direct incision and dissection of the rectus muscle due to the use of the pedicled TRAM flap. However, removing the rectus muscle, from which the pedicle arose would have defeated the purpose of the procedure.'

• Line 170, I am baffled it took days to discover the pressure sores, was there no check at the end of the procedure? If the position explains the buttock pressure sores, why did the patient also developed pressure sores on her heels. No heel pads in theatre? Prolonged reduced movement on ward due to delirium and body brace?

Reply 1: Thank you for your considerable comment.

Sufficient cushioning was provided on the surgical table, and additional sponges were installed on top of it without help pads, during procedure, pressure sores rarely occur. Even in cases of prolonged surgery, such sores are very rare, and we did not check for pressure sores immediately after surgery. However, it is regrettable that we did not check for pressure sores, and as a result, we have implemented a routine of adding additional foam padding and checking for sore areas in all surgeries since then. There was body brace but the patient untied herself and move around the whole floor because of delirium.

• Description of the case is long with a lot of irrelevant information. Needs to be re-written.

• Line 181, what does POM stand for ?post operative month

Reply 1: Thank you for your comment.

Yes, POM stand for post operative month. Thus we added the description for POM in manuscript. Thank you.

Changes in the text:

Page 9, line 15-16, In post operative month (POM) 1,

• The discussion needs to be rewritten with a significant amount of attention devoted to how this could have happened and how this will be prevented in the future (Check lists/ protocols), Prolonged operations should not be performed in a "sitting" position. If the aim is to acquire symmetry short term upper body elevation is sufficient to assess this.

• Conclusion need to be rewritten to reflect on poor practice

• Figure 3 – not sure what is meant with " pressure sores at site of vessel anastomosis"

Reply 1: Thank you for your delicate comment.

We agreed that it's not appropriate description. Thus we remove 'at the sites of vessel anastomosis' Changes in the text : page 19, line 1-2. Remove 'at the sites of vessel anastomosis'.