Author’s response to reviews

Title: ROTEM and Multiplate in four patients with abnormal routine coagulation studies before withdrawal of epidural catheters after major surgery: a case series.

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Author’s response to reviews: see over
Dear Editorial Board, Journal of Medical Case Reports

Thank you for reviewing our article. We hereby submit our revised version of:

**ROTEM and Multiplate in four patients with abnormal routine coagulation studies before withdrawal of epidural catheters after major surgery: a case series.**

Short title: Coagulation studies at epidural withdrawal

Owain D. Thomas, Anna Gustafsson, and Ulf Schött

As requested, we have moved the Methods section to after the Conclusions section and restated that we do not have any competing interests at the end of the manuscript. The most significant change that we have made is that we have tried to make the relevance of the cases clearer by adding what could be argued is a short ‘discussion’ to the case descriptions – that you did not consider the POC tests to be ‘showcased’ was a very much appreciated criticism which we have tried to put right here.

We address each of your comments in turn:

1. use a phrase "epidural catheter removal" instead of "withdrawal".

**Response:** we have used ‘removal’ instead of ‘withdrawal’ in the revised version.

2. The abstract needs to be re-written with data incorporated into the results section to make it understandable.

**Response:** We have added median values to both to the text and the abstract – the reason that we had previously chosen to show much of this data in graphical form only was to avoid ‘camouflaging’ important points with statistics of questionable significance but we do agree that we should include numerical data in the text.

3. In the introduction second paragraph the use of pre operative coagulation screening and post operative risk of bleeding should be referenced e.g. the BCSH guideline - Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures 2008.

**Response:** We have added a reference to Chee, Crawford and Watson (BJ Haematology, 2008). We have not removed the reference to Breivik in which there is also a clear list of risk factors, although we were pleased to see that there is actually a reference to Chee et al. by this list of risk factors for perioperative haemorrhage.
4. Introduction - I am not clear what ’normal bleeding history’ is?

We were referring to a lack of bleeding events in the history and have clarified this by instead writing:

“These tests’ [ie PT-INR/aPTT/Plc] usefulness is questionable in patients who lack risk factors for perioperative bleeding, such as a history of bleeding or taking anticoagulant drugs.”

5. The results really need to be presented more clearly.

Response: We have changed the results section so that each patient’s laboratory data is presented spatially nearer the case description. We have also rearranged and renamed the diagrams so that aPTT and PT’s trend towards hypocoagulability and Plc, ROTEM and Multiplate’s trend towards hypercoagulability is clearer. We have also précised the cases to some degree.

6. Normal ranges should be included for the lab tests PT, APTT etc and Multiplate, Rotem.

Response: These were already shown in the Table 1 or the Appendix. We have added normal ranges to the text at the first mention of each test.

7. I don’t feel the four case reports really show case the utility of the POCT to their fullest. These could be re-written.

Response: Although much of our research involves point of care tests we would certainly not advocate their routine use in situations for which they are not validated.

While we agree that we do not ‘show case’ ROTEM or Multiplate, we do think that the described cases bring up the very relevant point that these tests generally suggest hypercoagulability while PT and aPTT suggest hypocoagulability in the context of postoperative manipulation of epidural catheters. We believe that the use of PT and aPTT in particular often lead to delaying the removal of epidural catheters, which leads to delayed mobilization and an increased risk of infection.

In addition to clarifying the cases to some degree, we have inserted our most important point at the end of cases 2, 3 and 4.
8. There were a number of assay failures in the Rotem - what was this due to?

Operator error or faulty device or reagents?

**Response:** The error was not due to bad reagents since the assay failures were not consistent with changing ampoules of reagents.

In three patients there was a suspicion that the wrong activator had been used. These results were therefore excluded.

In one patient the curves were disrupted by artefacts which are caused by dessication of the surface of the sample causing clotting.

We think that our use of the word ‘missing’ was inappropriate here and so have clarified this in the text. We have added the following paragraph to the discussion:

It is significant that 18 of the 480 ROTEM results (4%) were excluded due to artefacts or suspicion that the wrong reagents had been used. Point of care tests have the limitation that they are often used by clinicians who are competent to interpret the results but who are neither trained to use nor experienced in using the equipment. Running ROTEM and Multiplate, for example, involve pipetting several different reagents giving the operator ample opportunity to use the wrong or contaminated materials or even the wrong blood sample. Some of these sources of error are eliminated by those hospital laboratories which have introduced ‘point of care’ tests with telemetry: samples are sent to the laboratory and run by trained and experienced technicians. Results are displayed in real time on a monitor at the ICU or operating theatres.

9. Blood was sampled from indwelling lines - was there contamination with anything that may have altered coagulation profile? Sampling from indwelling catheters is not routine in the UK, arterial lines in HDU/ICU.

**Response:** None of the lines in our study, other than the one described in case 2,
were treated with heparin or citrate.

Sampling from indwelling catheters is actually routine for most tests at our hospital, so we have added this to the methods section. We understand and agree that venepuncture is the gold standard and therefore suggest that we should avoid a long discussion over the pros and cons of testing from a non-heparinized central line or daily venepuncture during a prolonged hospital stay since this would have more to do with patient comfort and damage caused by venepuncture than POC coagulation tests.

10. If withdrawing from a central line the dead space volume x5 should be removed prior to taking a sample to avoid contamination.

Response: The volume of the Port-a-Cath system that we use is 1.3ml (this includes the part of the system between the port and the sampling syringe: subcutaneous chamber: 0.5ml; subcutaneous catheter with inner diameter 1mm: 0.1ml; attachment to sampling syringe: 0.7ml).

So the 10ml that we discarded before sampling in case 2 ought to have been ample. Nevertheless the sample was clearly heparinized, as shown by the ROTEM results, bringing in to question whether the ‘times 5 rule’ is enough. We have changed ‘bad sampling technique’ to ‘preanalytical error’.

Most of our tests were taken from normal central lines, though. We have regrettably not recorded which type of central line was used but most of these patients would have received a single-lumen CVC with an internal volume less than the Port-a-Cath system.

11. Why not also compare pre and post op point of care testing?

Response: Absolutely. We are currently running a study in which we are collecting routine, POC and coagulation factor levels pre-operatively and at the time of epidural removal.

12. I am not sure the association of platelet count and length of time following surgery is reliable without comparison to the pre-op platelet counts.

Response: We suggest that inclusion of Plc vs time in the report gives the cases validity since
clinicians who work with these patients regularly will recognize the pattern as representative. Since platelet count is generally used as a ‘stand-alone’ value in the context of deciding whether to remove an epidural catheter or not, we suggest that it is appropriate to display the platelet count without comparison to the preoperative value.

We do have preoperative platelet counts in 19 of the 20 patients (Range 173-352; Median 230). We do not, however, think that we should use too much space discussing the correlation between how long after the op the tests were taken and Plc, even though it is statistically significant: our study group is heterogenous and small in number; there is also the obvious confounder that patients who require epidural analgesia for two weeks are likely to have been subjected to a greater surgical insult than those who require an epidural catheter for three days.

13. Abbreviations used without explanation eg. COL, TRAP.

Response: We have made sure that the abbreviations are explained the first time they are used.

14. This case report also highlights the error rate with point of care testing in this case in the order of 13% which would seem high and make results for these techniques unreliable. Error rates would be higher in a unit that rarely used this technology. The availability of such techniques in UK largely restricted to cardiac surgical units. So context of potential change to practise limited. Please discuss.

Response: It should possibly be clarified that the number of missing ROTEM values was 18 out of 480, ie 4%, which is still high. The figure of 13% referred to how many of the ROTEM results indicated hypercoagulability.

It is an important point that error rates are high, also that ROTEM and Multiplate are somewhat cumbersome to carry out, involving several manual steps, which makes them time consuming and user-dependent. Out hospital laboratory is in the process of implementing centralisation of these tests (starting with ROTEM) – tests will be run at the hospital lab and results will be available in real time by telemetry at the ICU/theatres. With such a system in place the potential to use ROTEM and Multiplate in non-cardiac settings should be much greater.
15. There is an assumption of inflammatory response - was there any measure of an inflammatory response such as CRP?

**Response:** Yes we did record CRP on the day of epidural withdrawal when it had been taken as part of the patient’s normal care. This was the case in 16 of the 20 patients. Mean 83; Median 87; Standard deviation 47; Min 6.6; Max 138. FIBTEM indicates fibrinogen, which (like CRP) is an acute phase protein.

16. Perhaps an explanation of the techniques would be useful to add educational value to the case report.

**Response:** We have added an explanation of which tests were run and what they represent to the methods and an additional appendix. The appendix is actually very useful to have as a reference when interpreting ROTEM results.