Reviewer's report

Title: Spinal fusion leads to a statistical significant increase in serum titanium levels

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Reviewer: Thomas Johan Kibsgård

Reviewer's report:

- Major Compulsory Revisions

First of all, I think this is an important subject to study. What the authors want to show by this paper is well described in the introduction: (1) to detect a possible increase in serum titanium levels after spinal fusion and (2) to show a possible correlation between numbers of pedicle screws, cross connectors and interbody devices on serum titanium levels. They have a prospective study with a control group. But the study have some major shortcomings, some major negative elements follow.

The title; "Spinal fusion leads to a statistical significant raise in serum titanium levels" is a powerful statement and from the findings in the report I think this title is misleading.

Abstract: The background does not describe the purpose of the study, and the conclusion is to powerful, based on the study results.

Introduction: The introduction does not contain any information on normal Ti blood levels. The authors report a normal interval of 50-150 microg/L. Why a normal person has Ti in the blood is not discussed. The work from Kasai (ref nr 23) should be mentioned in the introduction.

The method:

1. Patients (poorly described) paragraph 2 and 3.
   The patient’s age, sex and fused segments are described. They report to different types of implant, but fail to report what type of surgery that has been done or what type of patients they are. Figure 2 is an anterior fusion, but I believe others have been used. The control group is not described. In table 1 there is a patient called nr 18. Are there any excluded patients?

2. Paragraph with the heading: Serum samples and titanium analysis. The Ti analysis is relatively well described, and a normal value 50-150 is reported. The precision of the test is not reported.

3. Statistical analysis. (poorly described)
   To compare the serum levels, two sample t-test were used (paired t-test? independent sample t-test?), but to set the level of significance to 0.05 is, in this
case, not right. The exact p-value should be reported. The heading is misleading when they report a significant raise in titanium level when the exact p value is 0.033 (paired t-test, 0.025 using two-sample t-test). This is not highly significant, especially in a small sample of 15. This limitation is poorly discussed. Are the preoperative data normally distributed?

The correlation analysis is not described at all in the method or in the results. The spread of the measurement are not commented, but I believe is SD.

The results

Paragraph 2: Mean Ti levels are presented. The exact p-value is missing. Missing data is not reported. There is a statistical significant increase in the Ti level, but 11 out of 15 have sub-normal levels of Ti and this fact is not reported. Six out of 15 had a Ti level of 2 at baseline. Are these results correct? Can we trust the Ti analysis?

Paragraph 5: The control group is 16 years younger than the patients. Why have not the authors chosen a control group that is more similar?

The main problem I have with this paper is the heading that states with great power: Spinal fusion leads to significant increase in serum titanium levels. They have a small sample, with a 26 level increase in serum Ti concentration. The p-value is 0.033 (which is not reported in the paper) and after 1 year the patients end in the lower part of the normal interval, which the authors have reported to be 50-150 (are these numbers correct?). This is almost the same as the control group that score 49. Why these controls have larger levels of Ti than the patients, at baseline, are not discussed. A clinical significant raise in serum Ti is, in my opinion, a value above the normal interval.

The data show that the patients have the same level of Ti as the normal control group and in the lower range of the normal population (50-150). At 1 year 11 out of 15 have subnormal levels of Ti, and no measurements are beyond the normal level. They do not convince me, with this paper, that Ti levels in these patients are abnormal and potentially harmful. The fact that the Ti level increases, has to be supported by the measurement precision or a description of a strictly standardized blood collection. If not, these finding, can be measurement errors. What are the precision of the Ti test? At baseline 6 patients have the value of 2. Are these measurements valid?

Paragraph 8: Main aim nr 2 is poorly reported in the method, results and in the discussion. When correlation is reported a correlation coefficient has to be reported together with the p-value.

Discussion

1. In the three first paragraphs the negative effects of Ti (or other metals) are discussed, but this is not studied and do not have to be discussed.
2. The findings are not properly discussed. In paragraph 5 in the discussion the
authors state that a significant raise after spinal fusions is seen. A significant elevated Ti level is, in my opinion, a Ti value above the normal interval.

3. Paragraph 6. In the discussion they state that there are a wide spread in the measurements, but fail to discuss the possible reasons. Can the spread be explained by the precision of the measurement? It is easy to perform a precision analysis and this should have been done.

4. Paragraph 8. They state that there is a significant increase in Ti levels between 3 and 12 months, and this is wrong.

5. Paragraph 9. You can not say that.

6. The limitations of the study are not properly discussed.

7. Another thing that are not discussed, and I do not understand; Richardson et al. (Travis) report levels that are 10 times lower than the authors. Why? They used the same method.

- Minor Essential Revisions
  The uses of paragraphs are too severe.
  Spelling has to be checked.

Figure 3
It would be better to have a 95% CI spread instead of SD.
Figure 4 and 5 should be replaced by correlation coefficient and p-value in the text.

Table 1.
Check headings (Präoperative). Why is the last patient nr 18? Are there any patients that were excluded?

Discretionary Revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests'