The usefulness of serum amyloid A as a post-operative inflammatory marker after posterior lumbar interbody fusion

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The post-operative changes in the serum levels of CRP and serum amyloid A (SAA) were investigated prospectively in 106 patients after posterior lumbar interbody fusion. In 96 patients who did not have complications related to infection within the first year after operation, the median levels of CRP before operation and on days 3, 7 and 13 after were 0.02 (0.01 to 0.03), 9.12 (2.36 to 19.82), 1.64 (0.19 to 6.10) and 0.53 (0.05 to 2.94) mg/dl, respectively and for SAA, 2.6 (2.0 to 3.8), 1312.1 (58.0 to 3579.8), 77.3 (1.8 to 478.4), 14.1 (0.5 to 71.9) μg/ml, respectively. The levels on day 3 were the highest for both CRP and SAA and significantly decreased (p < 0.01) by day 7 and day 13.

In regard to CRP, no patient had less than the reference level (0.1 mg/dl) on day 7. In only three had the level decreased to the reference level, while in 93 it was above this on day 13. However, for SAA, the levels became normal on day 7 in 10 cases and on day 13 in 34 cases. The ratios relative to the levels on day 3 were significantly lower for SAA compared with CRP on day 7 and day 13. Of the ten patients with infection in the early stages, the level of CRP decreased slightly but an increase in SAA was observed in six.

We concluded that SAA is better than CRP as a post-operative inflammatory marker.

Posterior lumbar interbody fusion for degenerative or isthmic spondylolisthesis may simultaneously resolve both the stenosis and instability. It is important to prevent post-operative infection as the occurrence of surgical-site infection (SSI) requires removal of the implant and may lead to catastrophic results. Better results are obtained following early diagnosis and treatment with antibiotics and debridement. Changes in the levels of inflammatory markers in the serum assist in the diagnosis of SSI. Many reports indicate that CRP is the most sensitive inflammatory marker, and infection should be suspected when the serum CRP level increases again after returning to normal levels.1-3 However, the CRP level may remain relatively high even when there is no infection.3,4 Consequently, if there are inflammatory markers which increase and then become normal more rapidly, they would be useful for the early diagnosis of post-operative infection. Serum amyloid A (SAA) is a protein that is a precursor of amyloid A protein which is deposited in the tissues in amyloidosis in cases of chronic inflammatory disorder. It is an inflammatory protein with the highest growth ratio, and in situations of stimulation such as stress immediate increases of up to a factor of 1000 of the serum concentration have been observed.5,6 This characteristic of the immediate increase is useful for the early diagnosis of an infection, and, in addition, SAA is of value for monitoring the effectiveness of treatment for infection because its half-life is short.6 However, its use as a post-operative inflammatory marker has not been described. Our aim was to investigate the changes in the levels of SAA after posterior lumbar interbody fusion and to compare SAA with CRP as a post-operative inflammatory marker.

Patients and Methods
Our study was prospectively implemented from April 2006 in patients who had single-level posterior lumbar interbody fusion using pedicle screws and fusion cages. The operations were for degenerative or isthmic spondylolisthesis and herniated lumbar discs. We excluded patients with a pyogenic or non-pyogenic inflammatory disorder.

After obtaining informed consent and entering patients into our study, we measured the white blood cell count, the serum CRP level (reference value, < 0.1 mg/dl) and the SAA level (reference value, < 8 μg/ml) before operation and on days 3, 7 and 13 after operation. We also recorded the daily body temperature before surgery up to day 14 after. The CRP and SAA levels were measured using a latex agglu-
tination reaction. Patients in whom the CRP and SAA levels increased again on day 7 or day 13, those in whom the body temperature returning to normal again exceeded 37°C and those in whom infection occurred within 12 months after operation were investigated separately as the SSI group. Patients without obvious SSI or any complications suggesting possible infection after 12 months were categorised as the normal group.

The diagnosis of SSI was made according to the criteria of the Center for Disease Control and Prevention and at least one of the following was present:

1. Purulent drainage from the deep incision, but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisced or deliberately opened by the surgeon when the patient had at least one of the following signs or symptoms, namely, fever (> 38°C), localised pain or tenderness, unless the site was culture-negative.
3. An abscess or other evidence of infection involving the deep incision found on examination, during re-operation or by either a histopathological or radiological examination.
4. The diagnosis of a deep incisional SSI by a surgeon or attending physician.

For all the patients, 1 g of cefazolin was administered intravenously 15 minutes before operation. If the surgery lasted for more than three hours, a further 1 g was administered. An additional 1 g was again given after surgery, but this was limited to the day of operation only. We completed the series at the end of February 2008 when the number of entries reached 100 cases.

The correlations and changes in the CRP and SAA levels were compared and investigated. In addition, since it was believed that the values of these inflammatory markers would involve individual differences among patients, we also investigated the ratios relative to the values on day 3 after surgery.

**Statistical analysis.** The Excel Statistics 2008 (Social Survey Research Information Co Ltd., Tokyo, Japan) software program was used for statistical processing. A p value of < 0.01 was considered statistically significant using the Spearman’s rank correlation test, Kruskal-Wallis test, and Wilcoxon matched-pairs test.

**Results**

The total number of patients entered was 106 (55 men and 51 women). Since not all of the data obtained showed a normal distribution, we used the median minimum and maximum values, quartiles and the 95th percentile as statistical values. The mean age at surgery was 65 years (18 to 88), and the mean body mass index 23.0 kg/m² (16.9 to 31.0). The mean operating time was 196 minutes (18 to 88), and the mean blood loss 164 g (30 to 570). The implants used were the Legacy (Medtronic, Sofamor Danek Co Ltd., Osaka, Japan) in 47 patients, the Mykres (Showa Ika Kohgyo Co Ltd., Toyohashi, Japan) in 45, the M8 (Medtronic) in 10 and the Xia (Stryker Japan KK, Tokyo, Japan) in 4. For the interbody fusion cage, the Telamon (Medtronic) was used in 72, the OIC (Stryker Japan KK) in 28, the Eivs case (Showa Ika Kohgyo) in three, the S-Telaman (Medtronic) in two and the Contact fusion case (Synthes) in one case. Four pedicle screws were used and cross-links were not used. Autogenous iliac bone was used as graft.

Of the 106 patients, SSI occurred in ten. It was obvious in five. In the other five the causes were not clear but antibiotics had been given because of further increases in the serum levels of CRP and SAA. These patients comprised the SSI group. The remaining 96 did not have any problems for up to one year after surgery and were therefore classified as the normal group.

In the SSI group two patients had pyrexia exceeding 38°C with white blood cell counts of 10 200 and 9300. Blood culture identified methicillin-resistant *Staphylococcus epidermidis* (MRSE) in each case. In the other eight patients, blood cultures were negative and the white blood cell count ranged from 4400 to 9100, with an increase in the temperature ranging from 37.0°C to 37.8°C. In four patients, the responsible bacteria (MRSE in two cases and *Staph. epidermidis* and *Staph. aureus* in one each) were detected at the surgical site. One patient was diagnosed as having SSI as there were progressive osteolytic changes around the cages on plain radiograph, which could not be explained by the inflammatory markers. In four of the five patients with obvious SSI, the CRP and SAA levels changed in a coordinated manner, but in the remaining patient, the SAA level increased again at an early stage while the CRP level decreased. In the other five patients, although a definite diagnosis of SSI had not been reached, we suspected infection because of the further increase in the inflammatory markers, and antibiotics were administered. In these patients, the CRP level remained unchanged or gradually decreased and only the SAA level increased again (Fig. 1). Antibiotics were administered for 28 and 36 days after debridement in the two patients with infection with MRSE, and for seven to 14 days in the other eight until all the inflammatory markers (white blood cell count, CRP, SAA and body temperature) and the findings on physical examination had reached normal levels.

In the normal group although significant correlations were observed between the serum levels of CRP and SAA on day 3, 7 and 13 after surgery (Spearman’s rank correlation, p < 0.001), the correlation coefficient decreased over time (Fig. 2). The mean and minimum and maximum levels of CRP before surgery and on days 3, 7 and 13 after surgery were 0.02 (0.01 to 0.03), 9.12 (2.36 to 19.82), 1.64 (0.19 to 6.10), and 0.53 (0.05 to 2.94) mg/dl, respectively, and for SAA 2.6 (2.0 to 3.8), 1312.1 (58.0 to 3580.0), 77.3 (1.8 to 478.0), and 14.1 (1.0 to 72.0) μg/ml, respectively. The values of CRP and SAA were highest on day 3 after surgery, and had decreased significantly on days 7 and day 13 (Kruskal-Wallis test, p < 0.001). There were no patients in whom the CRP level on day 7 after surgery became less than 0.15 mg/dl or the SAA level on day 7 became less than 5 μg/ml.
than the reference value (0.1 mg/dl), and the levels had decreased and reached the reference value in only three on day 13 after surgery. However, in regard to SAA, in ten patients the level became less than the reference (8 μg/ml) on day 7 and in 34 on day 13 after surgery. The median ratio of the CRP level on day 7 after surgery to that on day 3 after surgery, was 18.8% (5.2 to 64.0). For SAA it was 6.3% (0.1 to 34.0). On day 13 after surgery the CRP ratio was 6.2% (0.9 to 24.2) and the SAA ratio 1.3% (0.0 to 15.9). The SAA ratio was significantly lower than the CRP ratio on both day 7 and day 13 after surgery (Wilcoxon matched-pairs test, p < 0.001).

Discussion

SAA is a protein with a molecular weight of 12 000. In the blood it is present as a constituent apoprotein of hyperbaric lipoprotein (HDL), and its serum concentration increases by a factor of 1000 within 24 hours after stimulation such as stress. It has four isotypes (SAA1, SAA2, SAA3 and SAA4). SAA3 is not expressed in humans; SAA1 and SAA2 are acute-phase reactants which respond to inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor. SAA4 is a constituent protein of HDL and does not change during inflammation. SAA is mainly produced in the liver, but some studies have found that it is produced in other peripheral blood monocytes or endocapillary cells. The serum level of SAA reflects any inflammatory activity throughout the body, with the concentration increasing as inflammation becomes more severe and/or systemic, while remaining low in less severe or local inflammation. The serum levels of SAA fluctuate more perceptively and more immediately than those of CRP, and there are many reports in the cardiovascular and paediatric fields indicating that SAA can be used to monitor the effectiveness of treatment.

In our study, the serum levels of CRP and SAA were measured on day 3, 7 and 13 after surgery, and both had their highest values on day 3. Although the levels then decreased,
the rate of decrease of SAA was notable. Since further increases in inflammatory markers are important in the diagnosis of SSI, it is believed that this characteristic of an immediate decrease in SAA is useful. In our study, measurements were taken at three time points after surgery. If these had been implemented more frequently, the differences in the fluctuation of the levels of CRP and SAA may have been clearer. However, three post-operative measurements are adequate for screening.

In approximately 80% of the patients who were suspected of presenting with inflammation, the behaviour of SAA and CRP matched. The rate of expression of CRP-positive samples and SAA-negative samples was low and that of CRP-negative samples and SAA-positive samples was approximately 17%. In viral infections, fluctuations in the value of CRP are generally small, but in many cases increases in SAA have been observed. It is therefore believed that this is useful for distinguishing bacterial infections from viral infections as well as for monitoring. It has also been observed that during the administration of steroids, the serum level of CRP becomes low or negative, but that of the SAA is not affected. No gender or age differ-
ences have been noted.\textsuperscript{8,12,13} SAA is a better inflammatory marker with a larger growth rate than CRP. It shows no difference or gender or age and exhibits reactivity in patients including those with rheumatoid arthritis who are taking steroids. It can be considered to be a useful marker for assessing inflammation in patients who have undergone spinal surgery including posterior lumbar fusion.

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References