Postoperative changes of early-phase inflammatory indices after uncomplicated anterior cervical discectomy and fusion using allograft and demineralised bone matrix

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Abstract

Purposes We investigated sequential levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in uncomplicated ACDF (anterior cervical discectomy and fusion) using allograft and DBM (demineralised bone matrix) for primary cervical spondylosis and/or disc herniation. To our knowledge, there has been no study to investigate the diagnostic value of CRP and ESR for postoperative infection in ACDF using allograft and DBM.

Methods Blood samples of 85 patients, who underwent one- ($n=51$) or two-level ($n=34$) ACDF, were obtained and evaluated before surgery and on the first, third, fifth, seventh, 14th, 30th, and 90th postoperative days. No infection was found in any patient for at least one year follow-up period.

Results Mean CRP value increased significantly on the first postoperative day and reached a peak on the third postoperative day. The peak level rapidly decreased but remained elevated on the fifth, seventh, and 14th postoperative days. Mean ESR value increased significantly and reached a peak on the third postoperative day. The peak level gradually decreased but remained elevated on the fifth and seventh postoperative days. One- and two-level ACDF exhibited similar postoperative changes in CRP and ESR values and no significant difference in mean levels of CRP and ESR throughout the follow-up periods.

Conclusions This study demonstrates that uncomplicated ACDF using allograft and DBM showed significant abnormal values of CRP and ESR during the early postoperative period. This result suggests that abnormal

values of CRP and ESR in the early postoperative period do not indicate acute postoperative infection after ACDF using allograft and DBM. Straying from the normal course, such as a second rise or a failure to decrease, of CRP and ESR is more important to signpost acute postoperative infection in ACDF using allograft and DBM.

Introduction

Anterior cervical discectomy and fusion (ACDF) is an effective surgical procedure for the management of patients with cervical radiculopathy and/or myelopathy secondary to primary cervical spondylosis and/or disc herniation [1–5]. However, various types of ACDF-related complications may occur, which can be troublesome and occasionally catastrophic [6–9]. Among them, acute postoperative infection after ACDF, although very rare, is potentially dangerous and difficult to manage [6, 10–12]. Timely diagnosis and proper management of this potential complication are critical to accomplishing good outcome in these patients. However, it is difficult to detect acute postoperative infection after ACDF early because of vague clinical findings and inconclusive initial radiographic findings.

Autograft is a gold standard graft option for ACDF but has several disadvantages, such as donor site morbidities and limited availability [13, 14]. Therefore, allograft with or without demineralised bone matrix (DBM) have been recently used for ACDF and have achieved satisfactory clinical and radiological outcomes [15, 16]. However, allograft and DBM also have several disadvantages, such as risk of disease transmission and immune reaction [17–19]. Moreover, the incidence of postoperative infection after ACDF is reported to be higher in allograft compared to that of autograft [11].

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C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are early-phase inflammatory indices that have been widely used for early detection of postoperative wound infection after surgery because of their biological advantages, including rapid increase in concentration and a relatively short lag time [20–22]. CRP is reported to be superior to ESR for early detection of acute postoperative infection after spine surgery [23–28]. However, there has been no study to investigate the diagnostic value of CRP and ESR for postoperative infection after ACDF using allograft and DBM. Knowledge of the normal course of postoperative changes of CRP and ESR values after uncomplicated ACDF using allograft and DBM is a prerequisite to actually use these parameters as effective tools for early detection of postoperative infection after ACDF using allograft and DBM.

The authors therefore performed a study: (1) to investigate the normal course of postoperative changes of CRP and ESR values after uncomplicated ACDF using allograft and DBM as a baseline data, (2) to identify whether CRP is superior to ESR in the detection of acute postoperative infection after ACDF early using allograft and DBM and (3) to compare results between one- and two-level ACDF.

Materials and methods

A prospective study was performed in 103 consecutive patients who underwent one- or two-level ACDF using freeze-dried ulna ring allograft (Korea Bone Bank, Seoul, Korea) and DBX® (Musculoskeletal Transplant Foundation, Edison, NJ, USA) DBM for cervical radiculopathy and/or myelopathy caused by primary cervical spondylosis and/or disc herniation between January and October 2010. The patients who had previous anterior or posterior cervical spine surgery and previous infection history were not included in the study. Eighteen patients who had at least one abnormal value of CRP and ESR preoperatively were excluded from the study. Consequently, 85 patients were included in the final analyses. There were 40 men and 45 women with an average age of 55.2 years (range, 27–76 years). Fifty-one were one-level ACDF and 34 were two-level ACDF. There were no differences in demographic data, including gender and age, between one- and two-level ACDF ($p>0.05$), except for operation time (68.1 ± 14.7 min versus 93.7 ± 15.2 min, $p<0.001$) and total blood loss (42.3 ± 13.6 ml versus 54.9 ± 17.3 ml, $p<0.001$). The mean hospital stay was 5.6 days (range, four to seven days). None of the patients were given a blood transfusion postoperatively. In all patients, we confirmed the absence of infection by clinical evaluation (symptoms, signs, laboratory findings, and radiological findings) made with a regular follow-up schedule

(postoperatively, two weeks, one month, three months, six months, 12 months) for at least one year. This study was approved by the Institutional Review Board of our hospital and informed consent was obtained from all patients regarding use of their medical information for this study.

All ACDFs were performed by a single surgeon using the standard surgical technique using a left-side approach. DBX® DBM used 0.5 cc per level. Blood samples were obtained before surgery and on the first, third, fifth, seventh, 14th, 30th, and 90th postoperative days. Blood samples on the 14th, 30th and 90th days were obtained from patients in the outpatient clinic. Prophylactic antibiotic was given preoperatively (immediately before skin incision) and postoperatively for three days with first generation of cephalosporin.

CRP was measured using the latex agglutination turbidimetry on the HITACHI 7600 automatic analyser (Hitachi, Tokyo, Japan) according to the manufacturer's instructions, and the normal range was set to less than 0.3 mg/dL. ESR was measured using quantitative capillary photometry method on the TEST 1 system (Alifax, Padova, Italy) and the normal range was set to less than 15 mm/hour.

We performed paired *T*-test to investigate the postoperative serial changes of CRP and ESR values at each time to the preoperative level. In addition, we performed the comparisons of the mean values of CRP and ESR between one- and two-level ACDF using Student's *T*-test each time. Analyses were performed using SPSS for Windows statistical package (Version 12; SPSS Inc, Chicago, IL, USA) and a *p*-value less than 0.05 was considered significant. Finally, to determine whether CRP and ESR differed in temporal patterns of postoperative levels, we analysed the temporal pattern of postoperative changes of CRP and ESR levels by the level of changes calculated as the ratio of the value at each time to the preoperative value.

Results

Figure 1 demonstrated a normal course of postoperative changes of mean ESR values in uncomplicated ACDF using allograft and DBX® DBM throughout the follow-up period. Mean ESR value significantly increased and reached a peak level on the third postoperative day compared to preoperative level. The peak level gradually decreased but remained elevated on the fifth and seventh postoperative days. It decreased to below the normal reference level on the 14th postoperative day and returned close to the preoperative level only on the 90th postoperative day. One- and two-level ACDF exhibited a similar course of postoperative changes of mean ESR values and no significant difference in mean ESR values from the first postoperative day to the 90th postoperative day (Fig. 2).

Fig. 1 Normal course of postoperative changes of mean erythrocyte sedimentation rate values in uncomplicated anterior cervical discectomy and fusion using allograft and demineralised bone matrix. *** $p < 0.001$

Figure 3 demonstrated normal course of postoperative changes of mean CRP values in uncomplicated ACDF using allograft and DBX® DBM throughout the follow-up period. Mean CRP value significantly increased on the first postoperative day and reached a peak on the third postoperative day compared to preoperative level. The peak level rapidly decreased but remained elevated on the fifth, seventh, and 14th postoperative days. It decreased to below the normal reference level on the 30th postoperative day and returned close to the preoperative level only on the 90th postoperative day. One- and two-level ACDF exhibited a similar course of postoperative changes of mean CRP values and no significant difference in mean CRP values from the first postoperative day to the 90th postoperative day (Fig. 4).

Figure 5 demonstrated that the temporal change of mean CRP values was faster than that of ESR. The starting point of significant increase in mean CRP values was the first postoperative day while that of mean

Fig. 2 One- and two-level anterior cervical discectomy and fusion using allograft and demineralised bone matrix exhibit a similar normal course of postoperative changes of mean erythrocyte sedimentation rate values throughout the follow-up periods

Fig. 3 Normal course of postoperative changes of mean c-reactive protein values in uncomplicated anterior cervical discectomy and fusion using allograft and demineralised bone matrix. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

ESR values was the third postoperative day. The level changes of the mean CRP levels was much greater than that of the mean ESR levels. During the first week after surgery, the level changes of the mean CRP levels was 10 to 26 times compared to preoperative level while that of the mean ESR levels was one to three times compared to preoperative level.

Discussion

This study of uncomplicated ACDF using allograft and DBM for primary cervical spondylosis and/or disc herniation demonstrated that mean CRP values increased rapidly on the first postoperative day and reached a peak on the third postoperative day. After the peak, mean CRP levels rapidly decreased but remained at abnormal levels during the early postoperative period. Mean ESR values increased significantly and reached a peak on the third postoperative

Fig. 4 One- and two-level anterior cervical discectomy and fusion using allograft and demineralised bone matrix exhibit a similar normal course of postoperative changes of mean c-reactive protein values throughout the follow-up periods

Fig. 5 A schematic graph shows that changes of mean c-reactive protein values were much faster and greater compared to those of mean erythrocyte sedimentation rate values

day. After the peak, mean ESR levels gradually decreased but still remained abnormal during the early postoperative period. The temporal change of mean CRP values was faster than that of mean ESR values. The level of changes of the mean CRP levels was much greater than that of the mean ESR levels during the early postoperative period, especially the first week after surgery.

Postoperative infection after ACDF usually occurs within the early postoperative period, especially within the first few days and weeks [23, 24, 29]. Postoperative infection after ACDF poses difficult management problems, such as extensive long-term antibiotic therapy, re-operations, and a prolonged hospital stay. Early and accurate diagnosis is a crucial factor for successful management of postoperative infection after ACDF. However, it is difficult to actually detect acute postoperative infection after ACDF before the seventh postoperative day because clinical findings are vague and initial radiographic findings are inconclusive. Therefore, simple and reliable screening blood tests of early-phase inflammatory indexes, such as CRP and ESR, have been used to diagnose acute postoperative infection after spine surgery early. The CRP screening test is reported to be superior to ESR screening test for early detection of acute postoperative infection after spine surgery [23–28]. The results of our study suggest that a more sensitive parameter for enhanced immune responses elicited by ACDF using allograft and DBM appears to be the CRP because its level increased rapidly immediately after surgery, reaching a peak level followed by a decrease, and the level changes of the CRP levels was greater compared to ESR.

Kang et al. reported that close observation and appropriate medical management should be performed in a timely fashion when abnormal CRP responses are observed at five or seven days after surgery [24]. However, the results of our study suggest that even uncomplicated

ACDF using allograft and DBM enhances patients' immune responses considerably as does the surgery itself during the early postoperative period, especially the first week after surgery. Therefore, a significantly elevated level of CRP and ESR in the early postoperative period does not necessarily indicate the development of acute postoperative infection in ACDF using allograft and DBM. Rather deviation from the normal course, such as second rise or a failure to decrease, of CRP and ESR values is more relevant to the possibility of acute postoperative infection in ACDF using allograft and DBM.

According to previous studies, incidence of postoperative infection after ACDF varies between 0.1 and 3 % and is higher in allograft compared to autograft [11, 29]. Whereas autograft offers complete histocompatibility and virtually no inflammatory encapsulation of the graft material, various kinds of allograft will produce a spectrum of immunogenic responses from the host. The intensity of the immune response that occurs depends on the degree of enzymatic degradation of the native allograft protein. Human allograft is available in two forms: mineralised and demineralised [17–19]. Among the mineralised allograft, freeze-dried allograft is processed by removing water by a vacuum process and is less immunogenic. DBM is a type of allograft bone processed by decalcification of cortical bone. During the demineralisation process, all cellular elements as well as acid-soluble proteins are removed in order to eliminate immunogenicity. Therefore, DBM is weakly immunogenic. In our study, one- and two-level ACDF using allograft and DBM exhibited similar postoperative changes of CRP and ESR values throughout the follow-up period. There was no significant difference in mean levels of CRP and ESR between one- and two-level ACDF using allograft and DBM. These findings suggest that dose of DBM (0.5 cc and 1 cc) and number of allograft (one and two) used in one- and two-level ACDF makes no difference in immune responses due to weakened immunogenicity of freeze-fried allograft and DBM. Although uncomplicated ACDF using allograft and DBM significantly increased sequential values of CRP and ESR after surgery, the authors cannot say that use of allograft and DBM enhances immune responses compared to autograft because we did not have ACDF using autograft in our study as control. Further study is needed to investigate this issue.

In summary, this study demonstrates that uncomplicated ACDF using allograft and DBM showed significant abnormal values of CRP and ESR during the early postoperative period. These results suggest that significant abnormal values of CRP and ESR at some point in the early postoperative period do not guarantee development of acute postoperative infection after ACDF using allograft and DBM. Instead, deviation from normal course, such as a second rise or a failure to decrease,

of CRP and ESR is more important in the diagnosis of acute postoperative infection in ACDF using allograft and DBM.

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