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Intraoperative periarticular injection can alleviate the inflammatory response and enhance joint function recovery after hip arthroplasty in elderly patients with osteoporotic femoral neck fractures

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Abstract

Purpose: This study aimed to investigate the potential beneficial effects of periarticular injection (PAI) of multimodal drugs on the inflammatory response and joint function after hip arthroplasty in elderly patients with osteoporotic femoral neck fractures.

Methods: Fifty six elderly patients with unilateral osteoporotic femoral neck fractures were randomly allocated to 2 groups: the PAI group, which received the multimodal drug PAI intraoperatively before incision closure, and the control group, which received an injection of saline at the same time as placebo. The C-reactive protein (CRP), interleukin-1β (IL-1β), and IL-6 levels as well as the erythrocyte sedimentation rate (ESR) in peripheral venous blood samples were measured, along with the Visual Analogue Scale (VAS) score with activity and Harris hip score preoperation at 1, 2, 4, 7, and 14 days as well as 1 and 3 months post-operation.

Results: The 2 groups were comparable in sex and age, and no significant differences were observed in the preoperative CRP, IL-1β, and IL-6 levels, ESR, VAS score, or Harris hip score between the 2 groups (all $P > .05$). However, during the postoperative period, the PAI group exhibited significantly lower levels of CRP, IL-1β, and IL-6 as well as a lower ERS and VAS score compared with the control group ($P < .05$), while the Harris hip score was significantly higher postoperatively in the PAI group ($P < .05$).

Conclusion: Multimodal drug PAI can alleviate the inflammatory response and enhance hip function recovery after hip arthroplasty in elderly patients with osteoporotic femoral neck fractures.

Abbreviations: CRP = C-reactive protein, DVT = deep vein thrombosis, ERAS = Enhanced Recovery after Surgery, ESR = Erythrocyte Sedimentation Rate, HHA = hemiarthroplasty of hip, IL-1β = Interleukin-1β, IL-6 = Interleukin-6, PAI = periarticular injection, S.E.M. = standard error of the mean, THA = total hip arthroplasty, VAS = Visual Analogue Scale.

Keywords: hip joint function, inflammatory response, osteoporotic femoral neck fractures, periarticular injection

1. Introduction

The incidence of osteoporosis-related fractures of the femoral neck among elderly patients aged 65 years and older is increasing substantially with the continued growth of the aged population.[1,2] These injuries present not only an increased societal burden but also great challenges to orthopedists, given that many of the patients also suffer chronic conditions of the cardiovascular, pulmonary, and nervous systems and thus are at increased risk for mortality and loss of autonomy in activities of daily living (ADLs) than individuals without such conditions.[3,4] Hip arthroplasty combined with the Enhanced Recovery after Surgery (ERAS) protocol has become the preferred method for elderly patients.[5,6] However, a severe inflammatory response is common post-operation and increases pain at the operation site due to multiple factors such as surgical trauma.[7,8] Also, studies have shown that the systemic inflammatory response can cause cognitive dysfunction and delirium, which are associated with poor outcomes, including functional decline, prolonged hospitalization, institutionalization, and increased healthcare costs in elderly patients[9–11] as well as increase the risk of deep vein thrombosis (DVT) of the lower limbs.[12] Additionally, an increased preoperative C-reactive protein (CRP) level, particularly > 10.0 mg/dl, was shown to be associated with the 1-year mortality after hip fracture surgery in the elderly.[13] Such

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complications will eventually affect joint function rehabilitation and reduce treatment efficacy and patient satisfaction. Therefore, reducing the inflammatory response is a promising strategy for reducing pain following hip replacement and improving the early treatment efficacy. The levels of certain inflammatory factors during the postoperative period has been shown to reflect the inflammatory response.[14] Indeed, the roles of inflammatory cytokines in accidental trauma are well established, and the most commonly involved proinflammatory cytokines include CRP, interleukin-1β (IL-1β), and IL-6.[15–17]

A multimodal drug periarticular injection (PAI) was found to effectively relieve pain and promote better functional recovery postoperation among patients who underwent total joint replacement,[14,18] and previous studies verified that observation of changes in inflammatory factors following joint arthroplasty can help doctors identify and address abnormal indicators in a timely and accurate manner.[19–21] However, these previous studies focused primarily on patients with osteoarthritis or femoral head necrosis and rarely involved elderly patients with osteoporotic femoral neck fractures or the use of PAI in these patients. Thus, the influence of PAI on the changes in inflammatory factors that occur after hip arthroplasty in the elderly with osteoporotic femoral neck fractures remained unknown. To provide evidence for the best approach for treating patients with potential abnormalities, such as infection and DVT, during the postoperative period in a timely and accurate manner, the present study was performed to evaluate the effect of a multimodal drug PAI on the inflammatory response and joint function recovery after hip arthroplasty in elderly patients with osteoporosis-related femoral neck fracture.

2. Materials and methods

All experimental protocols applied in the present study were approved by the Institutional Review Board of Second Hospital of Yueyang (Hunan, China). According to the Declaration of Helsinki, written informed consent was obtained from all patients who participated in the present study.

In total, 56 elderly patients aged than 65 years or older with a unilateral osteoporotic femoral neck fracture who met all of the inclusion and exclusion criteria (Table 1[22]) were included in this study. The patients were randomly divided into 2 groups from July 2017 to October 2019. One group received multimodal PAI during hip arthroplasty, whereas the other group received a saline injection as placebo treatment during hip arthroplasty. Patients and nurses were blinded to the treatment group assignments.

Surgery in all 56 patients was performed by the same surgeon via the standard posterolateral approach. The surgery was performed using a laryngeal mask airway (LMA) and sacral plexus blocks with 100 mg Ropivacain (Naropin™). All patients were given 2 g of Cefotiam (LUOXIN Pharmaceutical Co., China) intravenously at 30 minutes prior to surgery and then given a further 2 doses within 24 hours after surgery. Tranexamic acid at a dose of 1000 mg was given intravenously at the onset of surgery, and 500 mg was given at the time of closure. A cemented cup (Combicup, LINK, Germany), uncemented stem (L.C.U., LINK), and ceramic head (Biolox Delta, Ceramtec, Plochingen, Germany) were used in total hip arthroplasty (THA), whereas a cemented stem (BC1, Chun Li, China), cement (PALACOS, Heraeus, Germany), and a bipolar head (Chunli, China) were used in hemiarthroplasty (HHA). The PAI group (32 hips with 28 cases of THA and 4 cases of HHA) received a multimodal drug PAI consisting of 15 ml of 10 mg/ml ropivacaine, 0.5 ml of 10 mg/ml morphine, 1 ml of 40 mg/ml parecoxib, 1 ml of 2 mg/ml compound betamethasone, 0.1 ml of 0.1% epinephrine, and saline to make up 60 ml in total before the incision was closed according to the literature.[23] The control group (24 hips with 21 cases of THA and 3 cases of HHA) received a placebo saline injection at the same time during operation. Celebrex (Pfizer, USA) at 200 mg p.o. BID and aminophenol oxycodone (SINOPHARM, China) at 330 mg p.o. PRN were used for postoperative analgesia. All patients were allowed to perform weight bearing and physical therapy activities on the same day as surgery.

In all patients, the levels of CRP, IL-1β, and IL-6 in peripheral venous blood as well as the erythrocyte sedimentation rate (ESR), visual analogue scale (VAS) score[24] with activity, and Harris hip score[25] pre-operation were evaluated on days 1, 4, 7, and 14 and then at 1 and 3 months post-operation. During this period, complications were evaluated. A peripheral venous blood sample was collected from each patient for measurement of the levels of CRP, IL-1β, and IL-6, as well as the ESR. The blood was centrifuged at 3500 rpm for 15 minutes at room temperature, and the obtained serum samples were sent for testing. The CRP level and ESR were detected by immunoturbidimetric assay (LEADMAN, China) and the Westergren method, respectively. Assays of the serum levels of IL-1β and IL-6 were carried out in duplicate using chemiluminescence kits (Human IL-1β kit and Human IL-6 kit, Hotgen, China).

2.1. Statistical analysis

The data are shown as mean ± standard error of the mean (S.E.M.). Comparisons between 2 groups were performed with an independent sample *t*-test and correlation analysis. All statistical analysis was performed using SPSS 22.0 (IBM SPSS, Chicago, IL). A P value $<.05$ was considered statistically significant. Data were plotted using Graph Pad Prism 8.0 (Graph Pad Software Inc., San Diego, CA, USA).

Table 1

Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age ≥65 years	Rheumatoid arthritis and other regional or systematic inflammatory disease
ASA-PS ≥3	Regional or systemic active infection
Single-site fragility fracture	Severe arrhythmia
Normal cognitive functioning	History of peptic ulcer and bleeding
No osteoarthritis or pain in the involved hip	Blood transfusion
No limitation in performance of daily activities before injury	Use of anti-inflammatory medications, e.g., aspirins, ibuprofen

ASA-PS = American Society of Anesthesiology Physical Status.

Table 2

Comparison of patient demographics between the two groups.

	PAI group (n = 32)	Control group (n = 24)
Age (years)*	71.28 ± 15.12	73.83 ± 7.87
Gender (M/F), n	12/20	10/14
ASA grade*	1.88 ± 0.79	1.88 ± 0.85
Operation (THA/HHA), n	28/4	21/3

* The values are shown as mean ± standard deviation.
ASA = American Society of Anesthesiology.

3. Results

The PAI and control groups were comparable in terms of demographics. The demographic data for patients in the 2 groups are presented in Table 2. Moreover, before surgical treatment, no significant differences were observed in the plasma levels of CRP, IL-1β, and IL-6 or the ESR, VAS score, and Harris hip score between the 2 groups of patients (all $P > .05$) (Table 3). All patients completed 3 months of follow-up, with the exception of 1 patient in the PAI group who was withdrawn from the study 1 week post-operation for a reason unrelated to surgery. One female patient in the control group experienced prolonged wound drainage from postoperative days 3 to 5 due to hypoalbuminemia, but periprosthetic infection was excluded according to the Assessment of the 2018 International Consensus Meeting.[26] No cardiac or central nervous system toxicities nor any other complication related to surgery was observed.

During the post-operative period, significant decreases in the plasma concentrations of CRP, IL-1β, and IL-6 as well as the ESR and VAS score were seen in the patients in the PAI group compared with those of the control group, while a significantly higher Harris hip score was observed in the PAI group (all $P < .05$ or $P < .01$) (Table 3). Notably, the peak values of CRP and IL-6 not only showed greater decreases, but also more rapid decreases than those in the control group. The CRP level was significantly lower in the PAI group than in the control group from 4 days to 2 weeks postoperation ($P < .01$), but at 1 month postoperation, no significant difference was observed between the groups ($P > .05$; Fig. 1). The ESR was significantly lower in the PAI group from 2 weeks to the end of the follow-up period of 3 months ($P < .05$ or $P < .01$; Fig. 2). The IL-1β level was significantly lower in the PAI group on days 4 and 7 post-operation ($P < .05$ or $P < .01$), but no significant difference was observed from 2 weeks post-operation ($P > .05$; Fig. 3). The IL-6 level was significantly in the PAI group than in the control group at 2 weeks, 1 month, and 3 months post-operation ($P < .01$), but no significant difference was observed before 2 weeks post-operation ($P > .05$; Fig. 4). The mean VAS score of the PAI group was significantly lower than that of the control group from 1 day to 2 weeks post-operation ($P < .01$), but then no significant difference was observed at 3 months post-operation ($P > .05$; Fig. 5). The Harris hip score of the PAI group was significantly higher than that of the control group only from 1 day to 2 weeks post-operation ($P < .01$), with no significant difference observed after 1-month post-operation ($P > .05$; Fig. 6).

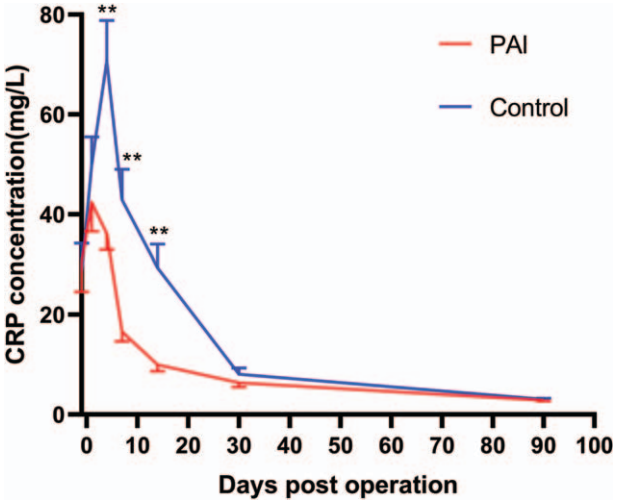

Figure 1. Changes in plasma CRP level. Data are shown as mean ± S.E.M. *$P < .05$, **$P < .01$ vs PAI group.

4. Discussion

Intraoperative PAI of multiple drugs has become an important procedure in perioperative pain control for total joint arthroplasty (TJA), a its efficacy has been proven by a series of

Table 3

Changes in CRP, ESR, IL-1β, and IL-6 levels as well as VAS and Harris hip scores.

Indicators	Group	Preparation	Day 1	Day 4	1 week	2 weeks	1 month	3 months
CRP (mg/L)	PAI	30.54 ± 6.00	42.33 ± 5.71	36.15 ± 16.55	16.55 ± 1.91	9.97 ± 1.31	6.35 ± 0.86	2.83 ± 0.16
	control	28.64 ± 5.60	49.92 ± 5.58	70.69 ± 8.11**	42.91 ± 6.11**	29.35 ± 4.68**	8.06 ± 1.28	3.04 ± 0.21
ESR (mm/H)	PAI	33.28 ± 4.77	40.08 ± 4.69	58.50 ± 4.77	50.28 ± 4.24	37.52 ± 3.84	25.74 ± 2.40	19.61 ± 1.13
	control	36.88 ± 4.84	40.08 ± 5.41	70.00 ± 4.52	66.63 ± 4.58**	53.71 ± 4.29**	35.50 ± 3.71*	22.71 ± 1.37**
IL-1β (pg/ml)	PAI	12.76 ± 5.98	18.93 ± 8.52	19.00 ± 6.71	10.80 ± 2.91	11.58 ± 4.72	5.19 ± 1.19	5.00 ± 0.00
	control	13.13 ± 2.70	38.27 ± 10.13	54.85 ± 18.18*	34.70 ± 9.64**	19.79 ± 5.32	11.96 ± 3.63	6.25 ± 1.03
IL-6 (pg/ml)	PAI	8.05 ± 2.49	11.09 ± 2.74	9.03 ± 2.08	5.74 ± 0.89	3.89 ± 0.21	3.43 ± 0.17	2.94 ± 0.17
	control	8.98 ± 0.87	15.01 ± 2.89	15.26 ± 5.08	9.24 ± 1.65	6.34 ± 0.69**	4.45 ± 0.31**	3.73 ± 0.17**
VAS score	PAI	6.71 ± 0.14	3.25 ± 0.78	3.06 ± 0.04	2.84 ± 0.12	2.26 ± 0.08	1.58 ± 0.10	0.83 ± 0.09
	control	6.96 ± 0.14	5.04 ± 0.11**	4.86 ± 0.14**	4.08 ± 0.10**	3.13 ± 0.10**	1.79 ± 0.85	0.96 ± 0.09
Harris hip score	PAI	100 ± 0.00	47.50 ± 1.13	55.16 ± 1.87	64.75 ± 2.07	72.88 ± 1.89	80.89 ± 3.60	87.82 ± 2.77
	control	100 ± 0.00	31.15 ± 1.06**	34.21 ± 0.83**	45.93 ± 1.06**	61.89 ± 1.58**	77.93 ± 5.01	89.93 ± 0.38

Data are shown as mean ± S.E.M.
* $P < .05$.
** $P < .01$ vs PAI group. C-reactive protein (CRP), interleukin-1β (IL-1β), interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), Visual Analogue Scale (VAS).

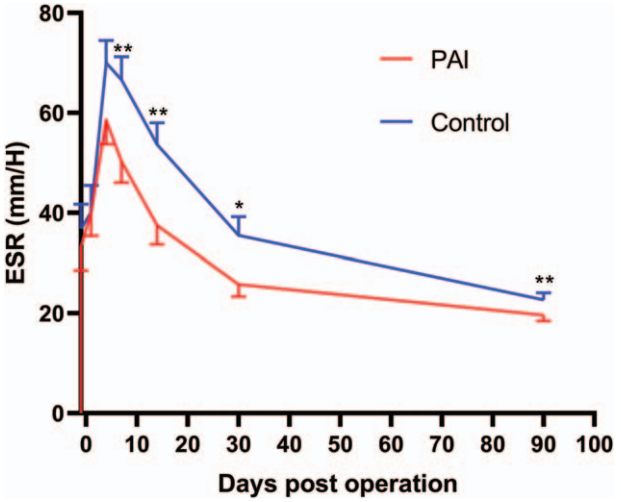

Figure 2. Changes in ESR. Data are shown as mean ± S.E.M. $^{*}P < .05$, $^{**}P < .01$ vs PAI group.

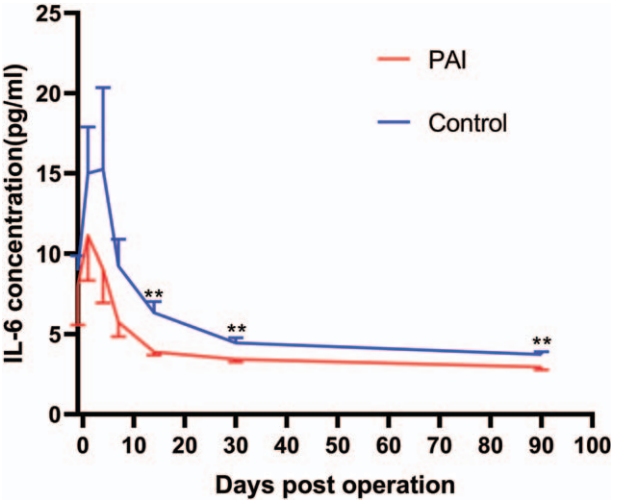

Figure 4. Changes in plasma IL-6 level. Data are shown as mean ± S.E.M. $^{*}P < .05$, $^{**}P < .01$ vs PAI group.

studies.[18,27,28] PAI can also reduce opioid consumption, which results in a better postoperative experience, including improved satisfaction and rehabilitation.[29,30] However, research to date has largely focused on the use of PAI during hip arthroplasty performed as treatment for osteoarthritis or femoral head necrosis, and the effects of PAI in elderly patients undergoing THA for osteoporotic femoral neck fractures remained unknown. Therefore, this study explored changes in plasma inflammatory markers, which may provide a reference for monitoring complications such as infections after THA performed with intraoperative PAI, in elderly patients with osteoporotic femoral neck fractures. Our results showed that patients who received intraoperative PAI suffered less pain during the first 2 weeks post-operation and recovered more rapidly, which is consistent with findings in patients undergoing THA for other causes.

In arthroplasty patients, rapid increases in these markers can be observed from 6 to 8 hours after orthopedic surgery, whereas the times required for the CRP level and ESR to peak and then to return to normal levels seem to vary. Prior studies reported that the plasma CRP level in patients with osteoarthritis or osteonecrosis undergoing total hip replacement or total knee replacement increases rapidly, reaching a peak value within 2 to 3 days after operation and decreasing rapidly thereafter, finally returning to normal by 2, 3, or 6 to 8 weeks postoperation.[19,31–34] More importantly, the CRP response has not been found to correlate with type of anesthesia, estimated blood loss, operative time, transfusion, medications, age, or gender, and as such, any late reversal of a downward trend should raise suspicion of infection and be a cause for concern.[16]

Following surgery without complications, the ESR usually reaches a peak level approximately 5 days post-operatively and

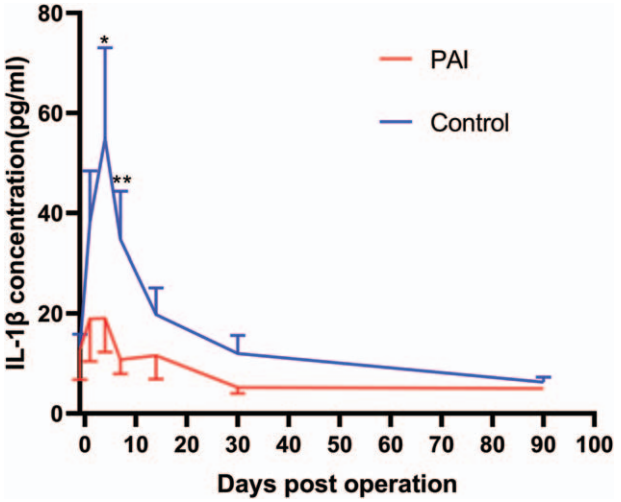

Figure 3. Changes in plasma IL-1β level. Data are shown as mean ± S.E.M. $^{*}P < .05$, $^{**}P < .01$ vs PAI group.

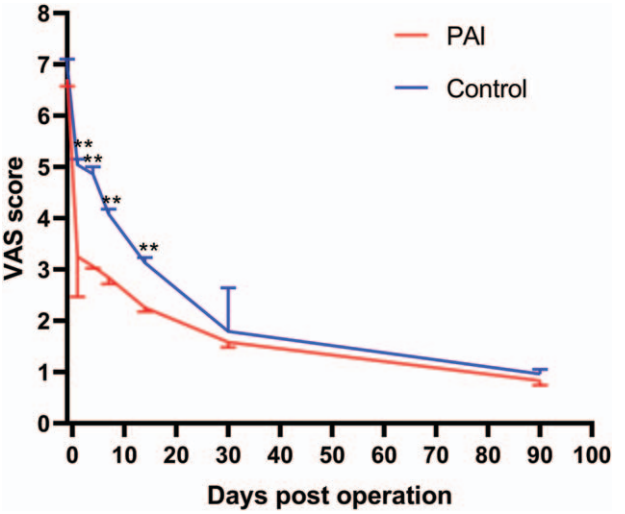

Figure 5. Changes in Visual Analogue Scale (VAS) score with activity. Data are shown as mean ± S.E.M. $^{*}P < .05$, $^{**}P < .01$ vs PAI group.

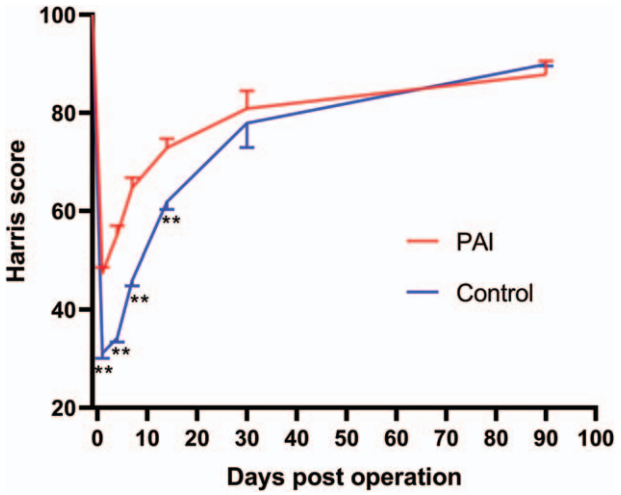

Figure 6. Changes in Harris hip score with activity. Data are shown as mean ± S.E.M. $^{*}P < .05$, $^{**}P < .01$ vs PAI group.

remains elevated for 3 to 4 months.[32–34] In contrast, another study reported a maximum ESR at an average of 1 month post-operatively with a return to normal levels within 3 to 6 months in 75 patients who underwent uncomplicated THA, but in 18 patients with deep infection, the ESR never returned to normal.[35] The results for both the PAI and control groups in our study are in agreement with previous studies in regard to the kinetics of CRP and ESR post-operation. However, the maximal values of CRP and ESR were significantly lower and decreased more rapidly in the PAI group than in the control group, and we believe these differences are closely related to the pharmacological effects of steroids and NSAIDs.

Very few studies have investigated IL-1β levels following hip arthroplasty in elderly patients. Clementsen et al[36] reported that systemic IL-1β was not significantly influenced by surgery at any time, with local values of IL-1β being higher than systemic values. However, they did find a rise in plasma IL-1β after severe trauma. In contrast, another study by Beloosesky et al[37] revealed that systemic IL-1β values were elevated in the first 7 days after operation and decreased by 1 month post-operation. According to Høgevold et al,[38] plasma IL-1β levels were very low preoperatively, during surgery, and after surgery. Through the benefits of the ERAS protocol and improvements in surgical techniques, no drainage tube was used in any patients in the present study, and thus, the local levels of inflammatory cytokines in the operation area could not be measured. Instead, systemic inflammatory cytokine levels were used to indirectly reflect the local levels of inflammatory cytokines. Our study suggested that systemic IL-1β levels were elevated preoperatively, intra-operatively, and postoperatively, reaching peak values on day 1 postoperation in both groups. The systemic IL-1β level then decreased gradually until returning to normal at 3 months postoperation. This prolonged elevation may have been due to severe trauma caused by both the fracture and surgery.

IL-6 is produced by various cell types, including muscle and immune cells, and has both pro and anti-inflammatory properties. Importantly in the postoperative context, IL-6 is a very sensitive indicator of inflammation and infection. Additionally, IL-6 is a modulator of osteoclast formation and bone resorption.[16,20] After hip injury, it has been reported that IL-6 is detectable within 60 minutes, and its concentration peaks between 4 and 6 hours.[37] Høgevold et al[38] that reported that the plasma IL-6 level increased postoperatively with a peak value at approximately 4 h after surgery in 12 patients undergoing THA. Clementsen et al[36] reported similar results in 10 patients undergoing THA. In additional studies, IL-6 levels reach peak levels in the first 6 to 12 hours following surgery and then returned to the baseline range by 48 to 72 hours postoperatively.[20,39] In the present study, peak values were observed on postoperative days 1 and 4 with a decreasing trend to preoperative levels by postoperative days 4 and 7 in the PAI and control groups, respectively, which is quite different from the observations in the studies mentioned above. This may be because we measured IL-6 at longer intervals, and the true peak levels occurred prior to testing, meaning that we did detect the actual maximum levels. Notably, no obvious decreasing trend was observed after the IL-6 concentration reached approximately 5 pg/ml at 1 month post-operation in both groups.

The results of the present study also indicated that PAI contributed to significantly better functional recovery[29] which may be related to reductions in the postoperative inflammatory response and pain level.

However, the present study has some limitations. First, the number of patients was small and a longer follow-up period is needed. Second, the length of hospital stay and adverse events, such as vomiting and nausea, were not investigated, although a previous meta-analysis found no differences in the postoperative nausea rate with PAI.[30] Further studies are needed to confirm these results in a larger population undergoing HHA with a more comprehensive analysis, including various sub-analyses.

5. Conclusion

Intraoperative multimodal drug PAI improves post-operative inflammation control and functional recovery in elderly patients undergoing THA for osteoporotic femoral neck fractures.

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Conceptualization: Zhizheng Xiong, Shuai Cao.
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