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Original Research Article

Negative pressure wound therapy with intermittent irrigation prior to debridement, antibiotics and implant retention in delayed periprosthetic hip infections

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ABSTRACT

Background: Infection control rate of debridement, antibiotics, and implant retention (DAIR) remains controversial. We aim to identify the influence of preoperative negative pressure wound therapy (NPWT) with intermittent pulsatile irrigation (IPI) on the efficacy of DAIR in delayed periprosthetic joint infection (PJI) hip cases.
Methods: 112 patients with delayed hip PJI were randomized into two groups. Group A included 53 cases treated with DAIR only whereas group B included 59 cases treated with NPWT and IPI followed by DAIR. Surgical invasiveness parameters, postoperative drainage, inflammation markers, and reinfection rate were evaluated in two groups.
Results: In group B, serologic and clinical inflammation markers decreased significantly than in group A, and major systemic or local adverse events were not observed during preoperative NPWT-based therapy. The duration of debridement and surgical invasiveness indices such as hemoglobin decrease were significantly lower in group B. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were significantly lower in group B until 3 weeks after DAIR. In group B, the duration of antibiotics administration was considerably shorter than in group A. In groups A and B, reinfection rates were 35.8% and 1.7% at the final follow-up.
Conclusions: Preoperative and postoperative NPWT could maximize DAIR's indication and success rate in delayed PJI cases.

Keywords: Negative pressure wound therapy, Delayed periprosthetic hip infection, DAIR

INTRODUCTION

Despite the advanced measures against periprosthetic joint infection (PJI), it still remains a demanding and challenging complication with incidence rate ranging from 0.3 to 1.9% in orthopaedic surgery.[1] With expected exponential increase in THAs performed in next decades, there will be a corresponding increase in the number of prosthetic hip infections.[2] Currently, new definition of PJI was established and early diagnostic markers are being assessed for availability in clinical field with advanced therapeutic options.[3] PJI can be classified into early (within 3 months), delayed (3 to 24 months) or late (greater than 24 months) according to the time of onset after insertion of the prosthesis.[3] Treatment options for PJI include long-term systemic antibiotic suppression, local antibiotic

delivery, debridement, antibiotics and implant retention (DAIR), one- or two-stage revision, resection arthroplasty, arthrodesis according to the phase.[3-6] One or two-stage revision is the time- or energy consuming procedure with large surgical invasiveness and thereafter it requires a long time of antibiotic regimen although they have a considerably higher success rate.[1,4-6] Conservative treatment options like systemic or local antibiotic delivery and DAIR have the advantages of lower cost, lower skill requirement and well-functioning prosthesis compared to revisions in early PJI cases.[7,8] Especially, DAIR has been focused by many authors as increasing number of cases treated with it in recent years albeit its infection control rate ranges between 10 and 100% in several studies.[9,10] Many studies over past decade have shown conflicting results with open DAIR. The overall infection control rate was reported as approximately 60% in a recent meta-analysis.[11] Nevertheless, it remains a traditional treatment option owing to the low cost and low morbidity of this treatment only in acute and early PJI cases. There have also been attempts to extend the limited indication of DAIR to delayed PJI cases by local antibiotic injection.[12]

In recent literature, negative pressure wound therapy (NPWT) for orthopaedic patients might accelerate wound healing without major complications.[13] There are accumulating data about successful application of NPWT in combat-related wounds, osteomyelitis, and skin grafts, although its application in deep infection or delayed PJI cases has been sporadically reported.[14,15] The mechanisms suggested by Ogrill et al are as follows: wound contraction, stabilization of the wound environment, decreased edema and removal of wound exudates, and microdeformation.[16] In order to extend the indication of DAIR which is considered to be relatively contraindicative for delayed PJI cases with sinus tract, we hypothesized that preoperative NPWT and intermittent pulsatile irrigation (IPI) using selected antiseptic solutions in combination with systemic antibiotic suppression (SAS, NPWT-IPI-SAS in total) would decrease the wound bacterial burden, infected tissue volume and surgical invasion, leading to increase the infection control rate when postoperative NPWT is accompanied.

Our objective in this study is to evaluate the influence of preoperative NPWT-IPI-SAS on serologic markers of inflammation, surgical invasion and drainage characteristics before DAIR, and compare the levels of serologic/clinical markers, duration of antibiotic administration and infection control rate in patients who received pre-/postoperative NPWT combination therapy with simple DAIR cases.

METHODS

We randomized 112 delayed PJI hip cases with fulfillment of inclusion criteria into two groups, who visited at the Arthroplasty Section, Clinical Orthopedics Institute, Pyongyang University of Medical Sciences for surgical treatment between February 2018 and August 2024. A total of 112 patients consisted of 53 patients (group A) who underwent simple DAIR with intraoperative irrigation by disinfectant solution and 59 patients (group B) who were treated with NPWT-IPI-SAS followed by DAIR. Inclusion criteria refer to ICM diagnostic criteria (2018): two major criteria including presence of sinus tract with the evidence of communication to the joint or visualization of the prosthesis and two positive growths of the same organism using standard culture methods; 7 minor criteria with various scores including - elevated C-reactive protein (CRP) (>10 mg/l for chronic infections) or D-Dimer (>860 g/l for chronic infection) (score 2), elevated erythrocyte sedimentation rate (ESR) (>30 mm/hour for chronic infections) (score 1), elevated synovial WBC count (>3000 cells/ml for chronic infections) or leukocyte esterase (++ for acute and chronic infections) (score 3), elevated synovial PMN% (>70% for chronic infections) (score 2), single positive culture (score 2), positive histology (score 3), and positive intraoperative purulence (score 3).[7] When one of 2 major criteria or minor criteria scoring ≥6 was fulfilled, PJI was confirmed. In the case with minor criteria scoring of 3 to 5, it was evaluated as possibly infected, whereas with minor criteria scoring of <3, it was confirmed as the absence of infection. Exclusion criteria were patients with less than 2 years of follow-up, coagulopathy and bone loss/fracture during surgical procedure. An Institutional Review/Ethics Board approval was obtained for the present study. We have obtained written informed consent for publication in print and electronic form from the patient. Characteristics of patients in present study were listed in Table 1.

Table 1: Patient characteristics.

Variables	Group A (n=53) (%)	Group B (n=59) (%)
Sex		
Male	40 (75.5)	45 (76.3)
Female	13 (24.5)	14 (23.7)
Age (years)	61±12 (49-74)	62±14 (43-76)
BMI (kg/m^2)	24.8±4.6 (21.2-30.8)	25.1±3.7 (21.9-28.8)
History of previous replacement		
THA	28 (52.8)	32 (54.2)
BHA	25 (47.2)	27 (45.8)
ASA score		
ASA 1	32 (60.3)	35 (59.3)
ASA 2	20 (37.7)	23 (38.9)
ASA 3	1 (2.0)	1 (1.8)

Continued.

Variables	Group A (n=53) (%)	Group B (n=59) (%)
Comorbidities		
Diabetes	8 (15.1)	9 (15.3)
Cardiovascular disease	3 (5.7)	4 (6.8)
Chronic liver disease	2 (3.8)	3 (5.1)
Chronic kidney disease	3 (5.7)	3 (5.1)
History of infectious disease	2 (3.7)	3 (5.1)
Mean interval time between index procedure and presence of sinus tract (months)	6.8±3.1 (3.2-10.7)	7.0±3.3 (3.4-11.2)
Duration of drain sinus (days)	15.1±7.5 (3-18)	16.2±7.3 (4-20)
Inflammation markers		
CRP (mg/l)	77.3±19.7 (39.3-104.2)	78.9±21.1 (40.7-106.4)
ESR (mm/hour)	45.2±13.2 (38-65)	46.7±17.2 (39-72)
WBC count (g/l)	10.34±2.64 (7.96-13.65)	11.83±2.81 (8.42-14.53)
Mean body temperature before initiation of therapy (°C)	38.4±1.2 (37.1-39.7)	38.5±1.1 (37.2-39.8)
Hemoglobin (g/l)	132.6±10.3 (109.6-147.4)	129.3±13.1 (107.2-148.4)
Albumin (g/l)	31.3±6.9 (25.4-38.3)	30.2±5.1 (24.6-36.1)
Infecting organisms		
Coagulase-negative *Staphylococcus*	25 (47.2)	28 (47.4)
Klebsiella pneumonia	13 (24.5)	15 (25.4)
E. coli	8 (15.0)	9 (15.3)
Pseudomonas aeruginosa	3 (5.7)	2 (3.4)
Streptococcus spp.	1 (1.9)	1 (1.7)
Culture-negative	3 (5.7)	4 (6.8)
Antibiotics regimen (pre-/postOP)		
CPX/GM/RFP	27 (50.9)	30 (50.8)
CTX/GM/CMX	14 (26.4)	16 (27.1)
LVX/RFP/MTZ	8 (15.1)	9 (15.3)
LVX/RFP/CMX	4 (7.6)	4 (6.8)
Follow-up (months)	70.2±34.7 (26-107)	70.5±35.1 (25-108)

[a]ASA: American Society of Anesthesiologists; CPX: ciprofloxacin; GM: gentamicin; RFP: rifampicin; CTX: ceftriaxone; CMX: cotrimoxazole; LVX: levofloxacin; MTZ: metronidazole; [b]continuous and categorical variables are reported using mean±SD (range)

There were no significant differences noted between two groups with regard to mean patient age, sex ratio, BMI, primary replacements, mean time between index procedure and presence of draining sinus, mean duration of sinus tract, mean body temperature, mean hemoglobin/albumin level, and inflammation markers (ESR, C-reactive protein, WBC). The American Society of Anesthesiologists (ASA) score was documented in addition to co-morbidities including diabetes, cardiovascular diseases, chronic liver diseases, chronic kidney diseases and history of previous infectious diseases. Coagulase negative *Staphylococcus aureus* and *Klebsiella pneumonia* were two most predominant species in group A and B (47.2%: 47.4%, 24.5%: 25.4%, respectively). There were 3 and 4 culture-negative cases respectively, in two groups. The antibiotic treatment was formulated based on the results of cultures and antibiotic susceptibility tests. In patients with negative cultures, treatment with antibiotics was determined based on our institutional empirical antibiotics guideline. In group A, only postoperative antibiotics administration was performed and pre-/postoperative antibiotics were given to group B. Ciprofloxacin/gentamicin/rifampicin was administered to 50.9% and 50.8% of patients, and ceftriaxone/gentamicin/cotrimoxazole regimen to 26.4% and 27.1%, respectively, in two groups. Minimum follow-up was 25 months with a mean follow-up of 70.2±34.7 and 70.5.2±35.1 months, respectively, in two groups.

Negative pressure wound therapy and intermittent pulsatile irrigation using alternate chlorhexidine and povidone iodide combined with systemic antibiotic suppression (NPWT-IPI-SAS) before DAIR was introduced to our institute since July 2015. Patients included in group A received simple debridement with methylene blue staining and pulse lavage using 8 to 10 liters of 0.9% saline solution followed by sterilization of component using mechanical washing and temporary immersing in the alcohol-based disinfectant cocktail, and SAS without any preoperative wound procedures. Drain was removed within 48 hours after simple DAIR in group A. In group B, all patients were placed on preoperative NPWT-IPI-SAS and same intraoperative procedures as group A except for dilute povidone iodide (0.3%) lavage followed by postoperative NPWT. Drain tube for preoperative NPWT consists of double-lumen tube separated by septum and limited length of balloon-inflating part on the outer layer. Outer portion is branched

into two tubes; one is for input and another one is for output during the irrigation. Insertion portion has one longer end for input tube during irrigation with side pores of 2 mm on various lengths and one shorter end for output with same-sized side pores. During preoperative preparation period, drain tube was inserted into sinus tract and then inflated balloon portion resulting in semi-occlusive environment of sinus entry. After that, iodophor-impregnated adhesive drape and polyvinyl alcohol sponge were used to achieve an effective vacuum favorable for drainage. Depth of tube insertion was determined with length in which tube was touched to prosthesis through fistulography. During NPWT-IPI, adhesive drape and sponge were exchanged every 48 hours. Intermittent pulsatile irrigation prior to DAIR was performed with drain tube placed in sinus tract. Pulse lavage unit was connected to input tube with open output tube to irrigate antiseptics solution for inner surface clearance of sinus tract which included 500 ml of 2% chlorhexidine gluconate solution for 3 minutes followed by 1 litre of saline solution and 500 ml of 3% povidone iodide solution for 3 minutes followed by 1 litre of saline solution. Finally, remove remnant of wound fluid completely and continuously applied wavelike pressure with maximal value ranging from -450 to -500 mmHg for 7 minutes and minimal one ranging from -50 to -75 mmHg for 3 minutes at 10-minute interval according to wound volume. DAIR was performed in patients of group B when they met 3 factors of following criteria: loss of redness/swelling, body temperature (<37 ℃), ESR (<35 mm/hour) and CRP (<30 mg/l). Before the reassembly of components, wound was soaked with 0.5% povidone iodide solution for 5 minutes followed by pulse lavage with 2 litres of 0.9% saline and finally NPWT was applied in group B. All surgical procedures were performed with modified posterior approach by one senior author and his arthroplasty team in which sciatic nerve was isolated directly for protection during extensive debridement. In group B, negative pressure of 125 mmHg was applied postoperatively for 5 minutes followed by -50 mmHg for 2 minutes at 7-minute interval which continues until drainage characteristics was serous liquid with transparent yellow color and met 4 factors of following criteria: drain output (<0.5 ml/hour), culture-negative, body temperature (≤36.5 ℃), WBC (≤5.0 g/l) with differential (neutrophil; 50-60%), ESR (≤30 mm/hour) and CRP (≤10 mg/l). In group A, drain for NPWT was removed at POD 3 regardless of aforementioned criteria.

We evaluated changes in mean body temperature, drain output and level of inflammation markers including ESR, CRP and WBC immediately before DAIR in group B. In addition to them, femoral girth was measured at the level of 20 cm proximal to superior margin of patella and then calculated reduction ratio by following formula.

$$Girth\ reduction\ ratio\ (\%) = (Pretherapy - posttherapy)/pretherapy \times 100$$

For evaluation of surgical invasiveness in two groups, duration of debridement, hemoglobin (Hb) loss, perioperative blood loss, transfusion and femoral girth change ratios were measured. Hb loss and femoral girth change ratio were evaluated at postoperative day 3 and 5 (POD3 and POD5), respectively and the later was calculated by following formula.

$$Girth\ change\ ratio\ (\%) = (Postop - preop)/preop \times 100$$

Blood volume was calculated by Nadler method and perioperative blood loss by Gross method.[17,18] Postoperative parameters included mean body temperature, mean duration of parental and oral antibiotic administration, and inflammation markers including ESR, CRP and WBC. Parental antibiotic administration discontinued when the patients met the following criteria: WBC (<5.0 g/l) with differential (neutrophil; 50-60%), ESR (<20 mm/hour) and CRP (<10 mg/l).

At final follow-up, reinfection rate was calculated by the percentage of patients who were confirmed as recurrent presence of PJI based on ICM diagnostic criteria (2018).[7]

Statistical analysis

Statistical analysis was performed using SAS version 14.2 software. The means of continuous variables were compared using t test (parametric) and proportions of a categorical outcome were compared using χ^2 (parametric). The significance level was established at 5%.

RESULTS

Anti-inflammatory efficacy of preoperative NPWT-IPS-SAS

Preoperative parameters of group B patients were summarized in Table 2. In approximately 90% of patients who underwent NPWT-IPS-SAS every 12 hours, the mean time to fulfill our criteria for DAIR was less than 11 days. Furthermore, in up to 95% of patients WBC, ESR and CRP were reduced by 46%, 29% and 37%, respectively, all of which were close to baseline. On the other hand, almost all patient demonstrated reduction of 4.2% and 40%, respectively, in body temperature and drain output compared to initial level whereas hemoglobin and albumin were reduced by 2.8% and 2.2%, respectively.

Minimizing debridement volume of NPWT-IPS-SAS prior to DAIR

Changes of parameters demonstrating minimization of infected tissue volume were listed in Table 3, which includes duration of debridement, Hb loss at POD 3, blood loss, transfusion and girth reduction ratio at POD 5. Mean duration of debridement by methylene blue staining was shortened significantly in group B than group A, which indicates minimization of infected tissue. In group B, Hb loss at POD 3 (drain removal day in group A), blood loss,

transfusion and girth reduction ratio at POD 5 were lower significantly than group A ($p<0.05$).

Influences of NPWT-IPS-SAS on postoperative changes of inflammatory markers

Postoperative parameters indicating the progression of postoperative inflammation were evaluated at 1 week, 2 weeks, 3 weeks postoperatively, which comprised CRP, ESR, WBC, neutrophil percentage and body temperature. CRP and ESR were significantly lower in group B than group A, however, WBC and neutrophil percentage did not show significant difference between two groups (Table 4 and Figure 1). Body temperature was significantly lower in group B compared to group A only at 1 week after DAIR and thereafter no difference was observed. Comparing CRP and ESR of patients in group B with uncomplicated elective THA patients (reference 28-31), CRP was a little higher than elective THA cases at 1 week postoperatively, which was similar to elective cases at 2 and 3 weeks postoperatively (Figure 1). Most patients showed transparent serous drainage since approximately 5 days after DAIR and constant decrease of drain output (Figure 2). Mean decrements of drain output were approximately 7 ml/day within 7 days after DAIR and thereafter 3 ml/day. In group B, NPWT drain was removed at the average of POD 10 ranging from 8 days to 14 days after DAIR when patients met drain removal criteria mentioned above. Mean durations of intravenous and oral antibiotic administration were 20 days (15-31 days) and 4 weeks, respectively, all of which were significantly shorter in group B than group A (6 weeks, 8 weeks; $p<0.001$).

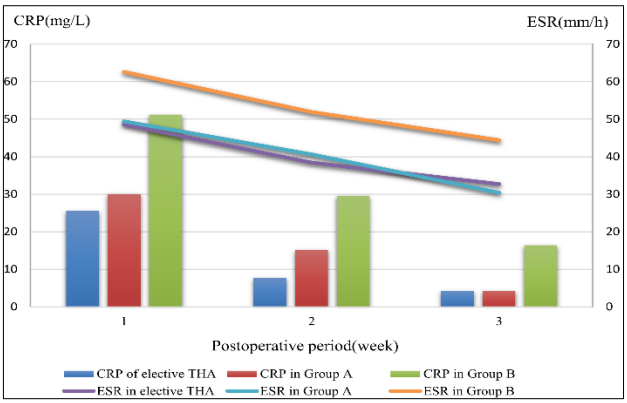

Figure 1: Comparison of postoperative CRP and ESR changes between NPWT cases and elective THA data from reference (19-22).

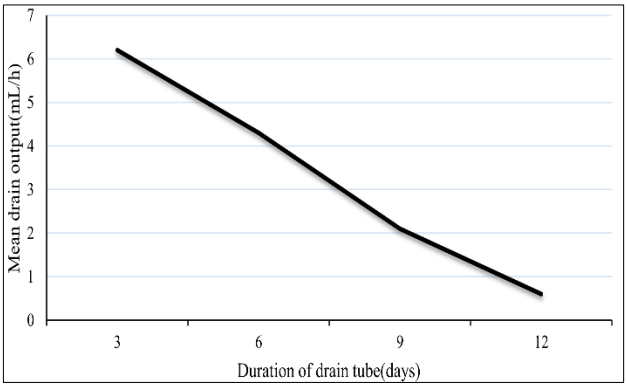

Figure 2: Changes of postoperative drain output in NPWT cases.

Table 2: Preoperative parameters of patients with NPWT-IPS-SAS.

Parameters	Mean±SD	Range
Duration of NPWT-IPI-SAS (days)	8.8±4.1	4-13
WBC count decrease (G/l)	4.8±1.7	3.5-6.9
ESR decrease (mm/hour)	13.4±6.3	10-31
CRP decrease (mg/l)	29.2±11.9	16.5-42.6
Body temperature decrease (℃)	1.6±1.3	0.4-2.8
Girth reduction ratio (%)	4.4±1.8	2.4-6.7
Mean drain output (ml/hour)	3.5±1.7	1.9-6.7
Drain output decrease (ml/hour)	1.4±0.4	0.6-1.9
Hb loss (g/l)	3.8±1.1	0-8
Albumin decrease (g/l)	0.7±0.4	0-1.5

WBC: White blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: hemoglobin

Table 3: Surgical invasion indices demonstrating volume of debrided tissue.

Parameters	Group A (n=53)	Group B (n=59)
Duration of debridement (minutes)	46±12	21±13*
Hb loss at POD3 (g/l)	19.5±6.1	10.1±3.2*
Blood loss (ml)	730±189	400±138*
Transfusion (ml)	680±239	250±198*
Girth change ratio (%)	8.6±3.8	2.4±2.3*

*Statistical significance below 0.05 when compared with group A

Table 4: Changes of post-DAIR inflammation markers.

Parameters	1 week		2 weeks		3 weeks	
	Group A	Group B	Group A	Group B	Group A	Group B
CRP (mg/l)	51.2±10.6	30.1±9.1*	29.6±8.7	15.2±4.3*	16.4±3.2	4.3±2.8*
ESR (mm/hour)	62.6±6.4	49.4±6.1*	51.9±5.7	40.6±5.3*	44.4±4.6	30.4±5.2*
WBC (g/l)	8.21±2.14	7.34±2.21	6.32±1.82	5.89±1.93	5.32±1.23	4.93±1.41
Neutrophil (%)	78±12	72±10	70±8	65±9	67±6	63±6
Body temperature (℃)	37.7±0.5	36.7±0.4*	37.2±0.6	36.5±0.3	36.9±0.4	36.4±0.3

*Statistical significance below 0.05 when compared with group A

We found no significant difference of Harris hip score at 3 months after DAIR between two groups [73 points (63-82): 71 points (67-80); p>0.05]. At final follow-up, we found 19 cases (35.8%) with recurrence of infection in group A and 1 case (1.7 %) in group B, which showed significant difference in reinfection rate between two groups (p<0.001). A reinfection case of group B had the causative organism of reinfection different from primary infection and it was a late PJI case due to hematogenous infection. In group A, all cases except for 2 negative-culture cases and 1 hematogenous reinfection case due to pneumonia had causative organisms same as primary infection, indicating the recurrence of PJI. PJI with MRSA occurred by nosocomial infection factor during treatment of contralateral diabetic foot of one negative-culture case who underwent two revisions and another one received two-stage revision with antibiotic-loaded spacer after recurrence of PJI during local and systemic treatment of psoriasis.

DISCUSSION

DAIR is known to be associated with the percentage of failures reported to be as high as 60%.[11,12] Nevertheless, DAIR remains an important element in the management of PJI, and many attempts continue to maximize its benefits and overcome pitfalls by combining various method.[3,4,6] Although there is limited literature supporting the application of negative pressure wound therapy (NPWT) in the management of PJI hip cases, its indications have been expanded constantly to other orthopaedic trauma wounds. Some shortcomings of recent surgical options for PJIs lead to search for several alternatives combined with negative pressure wound therapy in order to improve infection control rate. Especially, DAIR with simplicity and early functional recovery has been attracted author's intentions in the viewpoint of cost-effectiveness and infection-free efficacy. Our results suggest that preoperative intermittent pulsatile irrigation using antiseptic solutions and NPWT combined with antibiotic suppression could be feasible options to reduce the recurrence rate of infection after DAIR when postoperative NPWT is accompanied.

In debridement and irrigation with prosthesis retention, optimal irrigation solution and method is considered to be important in determining treatment outcome regardless of organism types.[14,15] *In vitro* studies suggested that pulsatile irrigation by various disinfectant solutions could reduce bacterial burden and biofilm production effectively.[14,23] Chlorhexidine and povidone iodide have proven to be effective in removal of methicillin-resistant *Staphylococcus aureus* biofilm through in-vitro biofilm model.[24,25] Nicholas et al suggested that 3-minute dilute betadine (0.35%) lavage was associated with reduction of acute deep infection after primary THA or TKA.[26] Furthermore, chlorhexidine was considered to be less toxic than the other antiseptics.[27] Based on preliminary study (not published) that alternate 2% chlorhexidine gluconate and 3% povidone iodide irrigation was identified as a safe and effective method for the infected wound with heavy bacterial burden, we selected them as irrigation solution. After antiseptics irrigation, its remnant was thoroughly removed to reduce adverse events related with them and we found no cases with hypersensitivity reaction.

Currently, NPWT improved treatment outcome in high energy trauma wounds, soft tissue defects and osteomyelitis.[28] Morykwas et al showed that negative pressure of 125 mmHg induce fourfold increase of blood flow in tissue surrounding a wound, resulting in accelerating the formation of granulation tissue in open wound or incisional wound, although applying -400 mmHg reduce the blood flow below baseline.[29] Furthermore, intermittent negative pressure for 5 minutes at 7-minute interval generated reactive increase leading to 40% increment of granulation formation.[29] However, this study was performed in superficial wound without heavy bacterial burden and therefore we could not extrapolate it to PJI cases because of different wound characteristics. Several studies supported that NPWT was effective in decreasing bacterial burden of infected wound.[29,30] Taking it into account that hip infection occurred in deep structure surrounding thick and extensile muscle layers with secretory synovial remnant, we designed preoperative NPWT with maximum pressure of -450 mmHg for 10 minutes and minimum of -100 mmHg for 2 minutes at 12-minute interval, regardless of microorganism species based on our institutional experience. All patients were placed on triple antibiotic regimen based on culture and antibiotic susceptibility test, current antibiotic guidelines and recommendation of our nosocomial infection control committee.[6,30] Culture-negative cases received empirical antibiotic regimen.

Mean duration of NPWT-IPI-SAS prior to DAIR was 8.8 days ranging from 4 to 13 days, when they met criteria for DAIR in group B. Criteria for DAIR were designed by

considering kinetics of inflammation markers in PJI cases (our institutional experience) and the other results.[19-22] Individual experience data demonstrated that acute phase of PJI was switched over to stable phase when body temperature, ESR and CRP were lower than 37 ℃, 35 mm/hour and 30 mg/l, respectively, without any swelling and redness. After the completion of pre-DAIR combination therapy, WBC, ESR and CRP were reduced by 4.8 g/l, 13.4 mm/hour, and 29.2 mg/l, respectively. Mean reduction ratio of femoral girth demonstrating swelling was 4.4% and body temperature was reduced by 1.6 ℃. Mean initial drain output was 6.2 ml/hour which was reduced by 1.4 ml/hour every 3 days to reach 3.5 ml/hour until DAIR was performed. For the evaluation of NPWT-related adverse events owing to bleeding and protein loss, hemoglobin and albumin loss levels were lower than 2.8% and 2.2%, respectively, which were clinically insignificant. Therefore, it was concluded that NPWT-IPI-SAS prior to DAIR could be a safe and effective measure to reduce levels of inflammation markers, resulting in stabilization of active infection.

Although its minimization effect of infected tissue could be evaluated indirectly by the change of inflammation marker levels and clinical features, it can be measured directly through surgical invasion indices including duration of debridement and parameters related with debrided tissue volume. Duration of debridement was approximately 25 minutes shorter lower in group B than group A. Mean hemoglobin loss at POD 3 and blood loss was 8.7 g/l and 326 ml, respectively, lower in group B than group A. In group B, blood transfusion rate was less than half of group A and more significant reduction of girth change ratio was observed in group A than group B, indicating that femoral girth was already reduced significantly before DAIR in group B. Because all DAIR procedures were performed by a senior author and his team, influences of procedure-related factors on results could be excluded and therefore infection tissue volume was confirmed objectively as being reduced by pre-DAIR combination therapy.

At 1, 2 3 weeks after DAIR, it was analyzed by inflammation markers such as CRP, ESR, WBC with neutrophil percentage and body temperature how pre-DAIR combination therapy influences on post-DAIR inflammation progression. CRP and ESR, dominant inflammation markers were significantly lower in group B throughout observation period than group A, which were close to the kinetics of marker levels in uncomplicated elective THA cases (Figure 1).[20-22] Of note, ESR and CRP levels were slightly higher in group B than markers' levels of primary THA cases which did not show statistical significance.[21,22] This indicates that NPWT-based therapy before and after DAIR could produce local tissue environment similar to primary THA by effective suppression of active infection. The mean drain output decreased to 50% of initial level at 2 weeks after DAIR and thereafter gradual decrement was shown (Figure 2). NPWT-drain output decreased markedly to less than 2 ml/hour within 10 days after DAIR and reached to less than or equal to 1 ml/hour since 15 days later. In group B, 22 cases (37.2%) met criteria for NPWT drain removal within 10 days after DAIR, which might imply effective reduction of post-DAIR inflammation markers by NPWT. With shortening of time to return to normal range of markers, duration of intravenous antibiotic administration was approximately 5 weeks shorter and oral antibiotics was 4 weeks shorter in group B than group A despite the application of the same treatment based on well-established recommendations.[3,30]

Although patients were only able to take static muscle strengthening and range-of-motion exercise on bed during post-DAIR NPWT drain, they demonstrated Harris hip score at 3 months after DAIR, similar to uncomplicated group A cases. It indicates that post-DAIR NPWT did not give any adverse influence on early functional recovery. Prolonged length of hospital stay did not overweigh the effect of this combination therapy, considering that re-hospitalization might cost much more than DAIR with short-term NPWT and irrigation.

Overall, reinfection rate was significantly lower in group B than group A (35.8%: 1.7%, $p<0.001$). A reinfection case in group B had hematogenous PJI which occurred at 69 months after DAIR during pneumonia complicated with diabetes mellitus. It is difficult to confirm that the recurrence was related with previous DAIR due to causative microorganism different from previous one. Excluding these interferences, reinfection rate could be interpreted as 30.2% and 0%, respectively, in group A and B, which demonstrates the possibility of the efficient application of DAIR with pre-/post-operative NPWT combination therapy in delayed PJI hip cases.

Present study has certain limitations. First, it is an institutional study with small sample size. Second, causative organism species and range of onset period were limited, resulting in difficulties to extrapolation of present study results to all PJIs. In spite of these limitations, present study clarified the infection control rate of NPWT-IPI-SAS followed by DAIR with post-DAIR NPWT in delayed PJI cases.

CONCLUSION

In patients with delayed periprosthetic hip infection, negative pressure wound therapy and intermittent pulsatile irrigation using chlorhexidine and povidone iodide combined with systemic antibiotic suppression followed by DAIR could reduce reinfection rate. Further large-scale studies are needed to determine if this combination regimen could improve the outcome of DAIR and there is possibility to expand its indication.

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