The Effect of Early Postoperative Physical Activity on Tissue Oxygen and Wound Healing

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Background. *Supplemented postoperative activity was compared to standard activity for effects on wound healing, subcutaneous tissue perfusion, and oxygen ($PscO_2$) following hip replacement (THR).*

Methods. *58 patients were randomized to standard post-THR activity (N= 27) or supplemental activity (N = 31) (arm and leg exercises, walking protocol). $PscO_2$ was measured with a microelectrode/tonometer system and perfusion determined by oxygen response. Healing was evaluated by (1) tissue cellularity, (2) mRNA for pro collagen, (3) hydroxyproline, and (4) DNA content obtained from a subcutaneous implant removed on the 7th postoperative day.*

Results. *Activity significantly increased DNA levels, but did not increase $PscO_2$, perfusion, cellularity, or collagen measures.*

Conclusions. *Healing measures were not improved with increased activity levels. However, activity did not reduce $PscO_2$ or wound healing. The majority of patients adhered to additional activity and tolerated the protocol well. Increased activity was associated with earlier discharge, suggesting other recovery-related benefits.*

Key words: *wound healing, tissue oxygen, surgery, physical activity*

More than 46 million surgical procedures are performed annually in the United States, requiring healing of injured tissues or wounds (Owings and Kozak 1998). Failure of wounds to heal contributes to morbidity and mortality. Avoidance of wound complications is thus essential to limit hospital stay and stem escalating health care costs (Ablaza and Fisher1998; Perencevich and others 2003). Promotion of surgical-incision healing includes therapies designed to prevent infection, such as aseptic, antiseptic, and antibiotic methods. Beyond these techniques, promotion of surgical recovery and wound healing may be improved by other therapies such as nutritional repletion, support of tissue perfusion, and early postoperative exercise. Yet, understanding of the effects of these management domains on wound healing and the mechanisms involved is largely undeveloped.

The value of postsurgical activity programs has been demonstrated by a reduction in the harmful ef-

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Support for this study was provided by a grant from the National Institute of Nursing Research, NIH, #R29 NR03510. The authors gratefully acknowledge Coralie Baker, Research Scientist, Environmental Health, University of Washington, and Sampath Narayanan, PhD, Research Professor, Pathology, Comprehensive Oral Health Research Center, University of Washington, for their contributions to the in situ tissue analysis. We thank Sylvia Pollack, PhD, Research Professor Emeritus, Biobehavioral Nursing and Health Systems, University of Washington, Seattle, for her helpful critique of this manuscript.

BIOLOGICAL RESEARCH FOR NURSING
Vol. 6, No. 2, October 2004, 79-89
DOI: 10.1177/1099800404268939

fects of bed rest and improvement in indicators of functional status and cardiovascular outcomes in various studies (Marshall and Hawrysio 1988; Nakai and others 1988; Basse and others 2002; Ragucci and others 2003). However, effects of postsurgical activity on wound healing have generally not been elaborated in such studies. Although there are few recent studies, earlier work on postoperative ambulatory activity or continuous passive motion (CPM) in animals showed increases in wound tensile strength (Newberger 1943; Stephens and others 1971; Van Royen and others 1986). Details of the mechanisms underlying this observation are largely unknown, but evidence suggests that physical activity may influence 1) the infiltration of cells that are important to healing (fibroblasts [FBs], macrophages [MPs], and polymorphonuclear leukocytes [PMNs]) to the wound area and 2) fibroblast biosynthesis of collagen, the main component of scar tissue.

Physical activity might improve wound healing through increases in perfusion and oxygen delivery to tissues. It has been known for some time that oxygen is a significant factor in the synthesis of connective tissue and resistance to wound infection (Niinikoski 1969; Hunt and Pai 1972; Hopf and others 1997). Blood flow and oxygen supply to skin and subcutaneous tissue are important in that these are common sites of surgical infection (Mangram and others 1999). Data on whether subcutaneous blood flow increases or decreases in response to activity are conflicting (Bulow and Madsen 1978; Hohimer and others 1983; Nielsen and others 1988; Whitney and others 1993).

Evidence derived from animal models indicates that higher levels of postoperative activity enhance wound healing (Newberger 1943; Stephens and others 1971; Van Royen and others 1986). Whether this is also the case in clinical populations or if it is related to effects of activity on subcutaneous-tissue oxygen levels is uncertain. Therefore, the purpose of this study was to test whether local tissue oxygen levels (partial pressure of subcutaneous tissue oxygen [$PscO_2$]) and wound healing responses (mRNA levels for pro α1[I] collagen; hydroxyproline accumulation, protein, and DNA; cellular composition) in tissue close to the surgical wound of patients having total hip replacement (THR) were improved by early, supplemental postoperative physical activity.

Literature Review

Postoperative Physical Activity and Wound Healing

Postoperative walking decreases the risk of deep vein thrombosis and improves pulmonary status, but little is known about its influence on other aspects of surgical recovery such as wound healing. An early study of 500 patients who had general surgery reported that there was no evidence to suggest delay in wound healing when ambulation was implemented on the 1st postoperative day (Canavarro 1946). Subsequent animal studies suggested that physical activity benefits wound healing by increasing wound tensile strength. Laparotomy wounds in rodents running 15 min daily on a treadmill reached maximum strength faster than wounds in rodents confined to cage activity (Newberger 1943). Stronger wounds have also been reported in rats allowed unrestricted activity in a large space compared to those confined in cages during the same period (Stephens and others 1971). CPM, although a different form of activity, produced statistically stronger periarticular skin wounds in animals, compared with similar wounds that were immobilized (Van Royen and others 1986). More recently, CPM was reported as preferable to active motion in patients with full-thickness cartilage defects (Alfredson and Lorentzon 1999). These observations of increased wound strength in the presence of greater physical activity suggest a positive effect on connective tissue formation, greater organization of the forming collagen matrix, or perhaps both. Although data from these animal studies suggest that activity benefits healing, none document specific responses of cells in the wound, collagen biosynthesis, and/or the physiologic mechanisms by which exercise may influence healing.

Physical Activity and Peripheral Perfusion

Increased sympathetic nervous activity in response to the onset of physical activity mediates blood flow and oxygen delivery to working muscles. Reports about the extent to which exercise enhances or limits perfusion, and thus oxygen availability important for healing in peripheral tissues such as subcutaneous tis-

sue and skin, have conflicting results. The documented differences in study outcomes could either enhance or inhibit healing tissue, depending on whether blood flow is maintained. Peripheral tissues are at risk of healing complications following injury particularly when perfusion to vital organs is preferentially sustained at the expense of peripheral circulation (Gosain and others 1991).

There appear to be regional differences in the distribution of blood flow to subcutaneous tissues during mild to moderate levels of exercise in normal humans and other primates. Blood flow to subcutaneous tissue during 4 min of mild dynamic leg exercise fell to 67% of resting flow rates in primates (Hohimer and others 1983). Subcutaneous perfusion during heel-raising exercises decreased in the arm but increased in the upper leg (Nielsen and others 1988). Experiments with prolonged bicycle exercise at workloads producing 50% of maximum oxygen consumption increased subcutaneous blood flow in the lumbar region 3-fold (Bulow and Madsen 1978).

Most studies focus on blood flow changes during activity, with less being known about subcutaneous blood flow responses following exercise. Elevations in blood flow to subcutaneous tissue above resting levels were reported in the hour after exercising at 50% of VO_{2max} (Bulow and Madsen 1978). In contrast, subcutaneous tissue oxygen and blood flow in healthy males were significantly lower 45 min to 1 h after cycling at 50% of VO_{2max} than during periods of strict bed rest (Whitney and others 1993). The effect of low- to moderate-intensity activity levels on subcutaneous perfusion in clinical populations has not been documented. Virtually no studies report on the effects of physical activity on subcutaneous perfusion in postoperative individuals. Improved understanding of physiologic responses to activity in clinical populations is needed to provide scientific rationale for activity prescriptions that potentially support perfusion and healing.

Tissue Oxygen and Wound Healing

Oxygen-enriched environments, in which participants breathe 35% to 70% oxygen, increase collagen synthesis in experimental wounds, whereas exposure to lower ambient oxygen concentrations decreases collagen synthesis (Niinikoski 1969; Hunt and Pai 1972). The amount of collagen measured in subcutaneous test wounds (5th to 7th postoperative day) of patients having general surgery is significantly related to wound tissue oxygen tension and perfusion in the 1st 48 postsurgical hours (Jonsson and others 1986). Angiogenesis and control of bacteria in healing tissues are also enhanced under conditions of increased oxygen availability (Knighton and others 1981). Recent data indicate that the level of oxygen in injured tissues is critical for the control of wound infections in general surgery patients (Hopf and others 1997). Significantly lower mean subcutaneous tissue oxygen tensions ($PscO_2$) have been documented in patients breathing 50% supplemental oxygen who subsequently developed wound infections (59 ± 12 mm Hg) compared with those who remained infection free (72 ± 18 mm Hg), indicating an optimum tissue oxygen level below which risk of wound infection increases.

Oxygen supply to tissue depends on adequate perfusion, and tissue oxygen tension falls as circulating volume decreases (Chang and others 1983; Jensen and others 1987). Several studies have used oxygen as an index of tissue perfusion, emphasizing both subcutaneous blood flow and $PscO_2$ as determinants of healing (Jonsson and others 1987; Jonsson and others 1991; Drucker and others 1996). Using $PscO_2$ as an index, subclinical reductions in subcutaneous perfusion have been reported in surgical populations; correction of reduced levels and increases in $PscO_2$ and perfusion are associated with improved healing (Hartmann and others 1992; Hartmann and others 1993). It is important to understand whether manipulating clinical therapies such as physical activity can improve the balance between oxygen supply and demand in injured tissues where molecular oxygen is used in cellular work required for successful healing.

Materials and Method

Design

A randomized, prospective, 2-group repeated-measures design was used. The study was conducted at 2 tertiary medical centers in the Pacific Northwest

after human subject review board approval was secured from each medical center. Using concealed randomization with varying block sizes stratified by gender, participants received standard or supplemented physical activity after THR. Standard care consisted of physical activity defined by care map and routine physical therapy for THR. Supplemented physical activity was based on enhancement of the standard activity protocol and consisted of isotonic arm exercises, isometric leg exercises, and a sequential protocol for increased ambulation starting on the day of surgery and extending through the 3rd postoperative day (Table 1). The standard activity program begins physical therapy on the 1st postoperative day but includes no arm exercises, walking does not typically begin until the 2nd postoperative day, and leg exercises are performed less frequently than in the supplemented program. Evaluators for all tissue analyses were masked to group assignment.

Table 1. Supplemented Activity Protocol

Day of Protocol	Supplemented Activity
Surgery	a. Active range of motion upper extremities every 2 h while awake. b. Gluteal, quadriceps, and calf exercises (10 repetitions) every 2 h while awake.
1st postoperative day	a. Upper arm strengthening exercises (10 repetitions) every 2 h while awake. b. Gluteal, quadriceps, and calf exercises (10 repetitions) every 2 h while awake. c. Walk in room or to chair for dinner.
2nd postoperative day	a. Upper arm strengthening exercises (10 repetitions) every 2 h while awake. b. Gluteal, quadriceps, and calf exercises (10 repetitions) every 2 h while awake. c. Walking (50 feet) in evening on unit.
3rd postoperative day	a. Upper arm strengthening exercises (15 repetitions) every 2 h while awake. b. Gluteal, quadriceps, and calf exercises (15 repetitions) every 2 h while awake. c. Walking (100 feet) twice on unit.

NOTE: Activities were performed in addition to all other physical activity including standard physical therapy following total hip replacement surgery.

Participants

Patients scheduled for THR were approached at a preoperative clinic appointment, informed of the study, and invited to participate. A standard process for obtaining informed written consent was followed. Enrollment criteria included 1) ability to speak and read English, 2) diagnosis of osteoarthritis (OA) or aseptic necrosis of the femur, and 3) freedom from the following: a) significant cardiac or pulmonary disease, b) mobility limitations related to arthritis in other joints, c) infection in an existing hip prosthesis necessitating the THR, and d) present use of beta-blocking drugs. Sixty patients with OA undergoing THR were enrolled consecutively. Sample size was based on power calculations using data from preliminary studies. The target sample of 28 patients per group ($N = 56$) was estimated to provide power of 0.81 for the cell studies, 0.96 for hydroxyproline, and 0.92 for oxygen and perfusion measures. One patient withdrew prior to randomization, and a 2nd (standard activity) withdrew from the study on the 1st postoperative day because of a request for removal of the subcutaneous catheters resulting in loss of tissue-related outcome data. The final sample consisted of 58 participants, 27 receiving standard activity and 31 receiving the supplemented intervention. Characteristics and comparability of the study groups on perioperative descriptive variables are shown in Tables 2 and 3. The groups did not differ statistically on any of the descriptive variables.

Procedures and Measures

Subcutaneous Tissue Oxygen

$PscO_2$ and perfusion were measured on the day of surgery and on the next 2 days with a commonly used micro-electrode-thermocouple tonometer system (Greif and others 2000; Arkilic and others 2003; LICOX CMP PO2 Tissue Oxygen Pressure Monitor, Gesellschaft fur Medizinische, Kiel-Mielkendorf, Germany). A silastic tonometer was inserted subcutaneously approximately 5 cm from the surgical incision after it was closed at the end of the THR procedure. A tunnel and small wound were created by the tonometer providing a consistent location for measuring tissue oxygen levels within tissue adjacent to the healing surgical wound.

Table 2. Characteristics of Patients in the Study Groups Reported as Frequencies

Characteristic	Standard Activity	Supplemented Activity
Ethnic background		
Caucasian	26	30
Asian	1	0
African American	0	1
Gender		
Female	13	12
Male	14	19
Diagnosis (leading to THR)		
Osteoarthritis	23	30
Other (e.g., aseptic necrosis, trauma)	4	1
Type of THR		
Cemented	17	19
Noncemented	10	11
Anesthesia		
General	6	7
Epidural	9	5
General and epidural	12	19

NOTE: THR = total hip replacement.

Table 3. Patient Characteristics Reported by Study Group (Mean [SD])

Variable	Standard Activity N	Standard Activity Mean (SD)	Supplemented Activity N	Supplemented Activity Mean (SD)	P Value
Age	27	65.5 (9.4)	31	66.0 (8.0)	0.84
Body mass index	27	26.8 (4.2)	31	29.5 (7.6)	0.14
Albumin	23	4.2 (0.3)	28	4.2 (0.3)	0.84
Transferrin	24	235 (44)	28	246 (39)	0.37
Smoking packs/years	26	14.6 (23)	27	9.7 (21)	0.17
Hematocrit DOS	24	32.0 (3.5)	28	33.9 (5.5)	0.13
Hematocrit day-1	25	30.0 (2.8)	29	30.6 (3.8)	0.54
Hematocrit day-2	25	30.5 (2.2)	27	30.8 (3.0)	0.77
Hematocrit day-3	14	30.7 (2.1)	20	29.8 (7.7)	0.66
IVF mL days 0-2	26	7718 (1895)	29	7873 (2220)	0.78
Estimated blood loss	27	503 (216)	31	569 (262)	0.30
Blood (units) DOS	27	0.8 (0.7)	31	0.5 (0.7)	0.11
Blood (units) day-1	27	0.4 (0.6)	30	0.5 (0.7)	0.93
Length of stay	27	5.4 (1.2)	31	5.4 (1.6)	0.48

NOTE: DOS = day of surgery; IVF = intravenous fluids. *N* varies because data were collected from the medical record where information was not always available, or in some cases, patients did not require treatment (e.g., blood replacement).

Subcutaneous temperature was measured simultaneously with $PscO_2$. The sensitivity, temperature coefficient of sensitivity, zero current, 12-h stability, and reaction time were determined individually for each electrode during production. The system has an error less than ±1% of true PO_2. $PscO_2$ levels were 1st measured while participants were breathing room air until a stable baseline $PscO_2$ was reached (stable within 1-2 mm Hg for 5 min); measurement continued while the participants breathed 50% oxygen. Breathing the increased oxygen concentration amplifies the tissue response and reflects perfusion to the subcutaneous bed. Maximum $PscO_2$ achieved on oxygen was recorded when a stable value was achieved. Two additional measurements were made on each of the next 2 days between 1300 and 1700 hours. Measurements were performed prior to or at least 30 min after physical therapy or ambulation. After the final measurement, the silastic catheter was removed.

Perfusion

Perfusion scores were calculated based on $PscO_2$ data and the response to breathing oxygen at each measurement. Briefly, perfusion calculations are based on the Fick principle. $PscO_2$ increases as arterial oxygen increases during breathing of supplemental oxygen provided that perfusion is maintained. Normal extraction of oxygen by subcutaneous tissue is 0.7 mL per 100 mL of blood (Gottrup and others 1987). However, if perfusion decreases, oxygen extraction increases and there is a reduction in $PscO_2$. A lack of response to breathing increased oxygen is indicative of an increase in extraction and poor perfusion (Jonsson and others 1987). In this study, a 20% increase in tissue oxygen from baseline scored as 1 and a lesser response scored as 0. Calculating tissue oxygen response using this method is a relative, not absolute, measure of perfusion. Interpretation of the response is based on the fact that increases in $PscO_2$ will occur as long as oxygen extraction is low and perfusion excellent (Jonsson and others 1991).

Wound Healing

Wound healing was evaluated by analysis of tissue cellularity, mRNA for pro collagen, and hydroxyproline obtained from a subcutaneous implant of sterile

expanded polytetrafluoroethylene (ePTFE) that was removed on the 7th postoperative day. The ePTFE tube was placed parallel to and 2 cm from the tonometer at the end of the surgical procedure. It is possible to test healing response, as the 90- to 120-μm pore size of the ePTFE material permits cell entry, deposition of connective tissue, and subsequent angiogenesis. This technique provides the opportunity to study cellular responses including measures of the newly forming wound matrix. This method thus has an advantage over other measures (e.g., visual observation, collection of wound fluid), where objective measurement of collagen production is not possible. No complications were associated with any of the ePTFE implants. One end of the tube was left exposed and sutured to the epidermis allowing retrieval. After removal, a 1-cm length was sectioned from the center of the tube, placed in 10% formalin, embedded in paraffin, and processed for histology and in situ hybridization; another 1-cm section was sectioned for DNA analysis; and the remainder of the tube, left for hydroxyproline assay, was stored at –20 °C. Tissue samples were thawed and dried at 60 °C for 24 h before the biochemical analysis.

Cellular Response

Samples for histology were cross-sectioned into 8-micron sections. The slides were stained with hematoxylin and eosin for identifying infiltration of granulocytes, MPs, and FBs. Other sections were stained with Masson's trichrome to evaluate formation of connective tissue in the wound matrix that formed within the ePTFE tube. A pathologist masked to group assignment evaluated stained sections. Sections were evaluated for cellularity using a semiquantitative scale rating presence of PMNs, MPs, FBs, loosely organized connective tissue, and organized connective tissue. Possible scores ranged from 0 to 3 (0 = no cells, 1 = scant cells, 2 = moderately extensive with 50% or less of the histological field filled at low power and all of the field filled at high power, 3 = extensive cells, histological field filled at low and high power).

mRNA for Pro α1[I] Collagen

A 1.8-kb cDNA coding for human pro-1(I) chain of type 1 procollagen (Hf677) was subcloned in pcDNA3 (Invitrogen, Carlsbad, CA). The plasmids were linearized with Hind III and Not I and transcribed into both antisense and sense (negative control) riboprobes in T7- or SP6-primed reactions with the Combination Riboprobe System (Promega, Madison, WI) and 35^S-UTP (New England Nuclear, Boston, MA) (Chu and others 1982; Bernard and others 1983).

The in situ hybridizations of paraffin sections were carried out as described previously in detail (Stokes and others 2001). Pretreated slides were hybridized overnight at +50 °C, and high stringency washings and ribonuclease A (Sigma, St. Louis, MO) treatments were performed to remove nonspecific binding of the probe. The posthybridization procedures were followed by autoradiography with an NTB-3 emulsion (Eastman Kodak, Rochester, NY). The slides were exposed under light-safe conditions at +4 °C for 8-12 days. The slides were then developed in Kodak D-19 developer (Eastman Kodak) and counterstained with hematoxylin and eosin. For negative controls, simultaneous hybridization with the sense riboprobe was performed on replicate tissue sections. For analysis, positive cellular labeling was defined as 5 or more silver grains in a single cell. A scoring system with the following categories was used: many positive cells or many areas with positive cells or dramatic positive cells; several positive cells or several areas with positive cells; rare but several clearly positive cells; no positive cells when there are enough cells present to make a determination; insufficient cells present to make a determination.

Hydroxyproline

The method for the determination of hydroxyproline was modified from Woessner (1961) and Grant (1964) and redesigned for microplates and EIA reader. Fifty μl of blank, standard, or test samples were pipetted into microplate wells to which 50 μl of the Chloramine T were added. The plate was tapped to mix and incubated (covered) at 37 °C for 20 min. Following incubation, 50 μl of the HClO4 was added; 100 μl of the PAB was then added, and the plate was again mixed by tapping. The covered plate was placed in a 70-80 °C oven for 20 min. After cooling, the absorbance at 550 nm was measured in a Bio-Tek Instruments EIA reader. Data were linearly regressed using

Microsoft Excel™, and the hydroxyproline in the unknowns was calculated from the regression curve.

DNA

The ePTFE sample processed for DNA was extracted for 30 min in 1.0 ml of 0.5N $HCLO_4$ at 4 °C. The fluid was removed and replaced with an additional 1.0 ml of 0.5N $HCLO_4$, and the sample was extracted at 100 °C for 30 min. The extract was cooled and divided into 2 aliquots for DNA determination by the method of Burton (1956). One milliliter of diphenylamine reagent was added to each aliquot. The samples and native DNA standards were prepared identically and incubated at room temperature overnight. Absorbance was measured against a reagent blank at 600 nm, and DNA content was determined by regression analysis of the standards. Sample analyses were performed in duplicate.

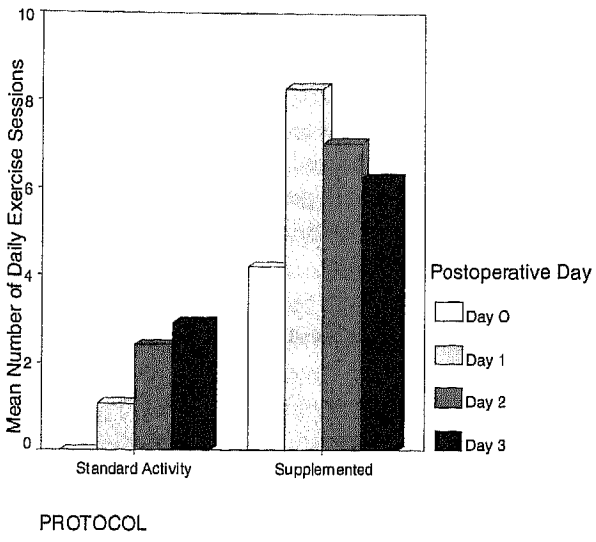

Figure 1. Patient performance of lower-extremity exercises postoperative days 0-3.

Evaluation of Activity

Postoperative walking distances and frequency of upper- and lower-extremity exercises were determined from daily entries on the medical record physical therapy progress form and bedside activity diary entries made by the participant, primary nurse, and the research team. The walking distances for supplemental activity were defined by the study protocol (Table 1); however, patients were not limited by the prescribed distance. Those who chose to walk further were allowed to do so. Participants in both groups were seen twice daily for the 1st 3 postoperative days by an investigator. At each visit, information on the bedside activity diary was verified. A standard rolling tape measure was used to verify all distances walked. Eighty percent (25/31) of the participants in the supplemented activity group were able to adhere completely with the activity protocol. Of the 6 participants who did not meet 100% adherence, 1 was unable to complete the protocol and the remaining 5 achieved between 19% and 85% adherence to the prescribed activity. Weakness and fatigue were the main reasons that these 6 patients were unable to fully achieve prescribed walking distances. During the 1st 3 postoperative days, participants in the standard activity group walked an average of 939 feet (± 882) compared with an average distance of 1896 feet (± 2407) for those in supplemented activity. Because the data on walking were skewed, a log transformation was performed to normalize the distribution. A test of the difference in mean walking distance between the 2 groups of this log transformation showed the activity group walked significantly further distances (Mann-Whitney U = 271, P = 0.021).

Figure 1 displays the number of times each day that participants in the 2 groups performed lower-extremity exercises. As shown in the figure, those in the supplemented activity group performed more lower-extremity exercises. Patients receiving standard care performed leg exercises as guided by standard postoperative physical therapy and performed virtually no arm exercises because these are not routinely prescribed. T-test evaluation of the group differences of the number of sessions for both arm and leg exercises showed that the supplemented activity group had significantly higher values on all days ($P < 0.001$ all tests). Analysis of walking distances and frequency of performing arm and leg exercises indicates that the integrity of the intervention was maintained, successfully delivered, and performed by participants assigned to the supplemented activity protocol.

Data Analysis

Descriptive statistics were used to characterize the sample. Differences in DNA and protein in the ePTFE samples were examined using the Mann-Whitney *U* test. Chi-square was used to evaluate mRNA, cell composition, and tissue perfusion responses. Tissue oxygen data were analyzed using repeated measures analysis of variance.

Results

Pro α1[I] Collagen

Results for mRNA are based on in situ hybridization and evaluation of mRNA expression using the semi-quantitative scale. Frequencies by level of expression were as follows (standard activity/supplemented): no message 6/6; rare message 1/0; several positive cells 2/4; many positive cells 16/16. Samples from 7 patients had insufficient tissue present to evaluate. There were no significant group differences for presence of mRNA message in the ePTFE samples ($\chi^2 = 2.689, P = 0.611$).

Hydroxyproline, Protein, and DNA Accumulation

There was no difference between groups on the amount of hydroxyproline content present in the ePTFE samples, expressed as μg per cm of ePTFE tubing. Mean values were 0.50 for standard activity (± 0.25; 95% CI, 0.40 to 0.60) and 0.43 for supplemented activity (±0.15; 95% CI, 0.38 to 0.49), $t = 1.2$, $P = 9.22$. In addition to hydroxyproline, the ePTFE samples were analyzed for accumulation of protein and DNA, both expressed in mcg per cm of tubing sample. The groups had similar amounts of protein (44 ± 20, 95% CI 36-52 standard activity; 49 ± 20, 95% CI, 41 to 57 supplemented activity; $P = 0.25$, Mann-Whitney *U* test). The supplemented activity group had significantly higher amounts of DNA (9 ± 7, 95% CI, 7 to 14) compared with standard activity (12 ± 7, 95% CI, 8 to 15; $P = 0.04$, Mann-Whitney *U* test). Figure 2 displays mean DNA differences between groups.

Cell Composition

Groups did not differ significantly on histological ratings of cellularity and presence of connective tissue. The supplemented activity group had a slightly higher presence of FBs and MPs than the standard activity group ($\chi^2 = 7.17, P = 0.06$ and $\chi^2 = 7.50, P = 0.11$, respectively).

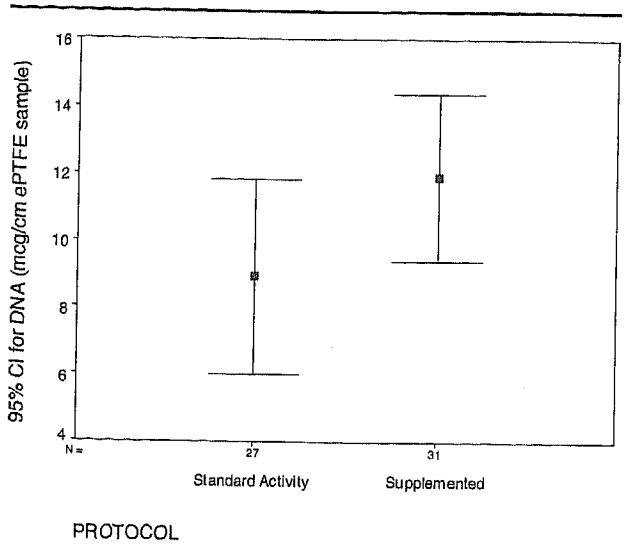

Figure 2. Mean differences in DNA content of ePTFE (expanded polytetrafluoroethylene) tissue samples between study groups.

Tissue Oxygen

$PscO_2$ data were available for 25 participants in the standard activity group and 26 participants who received supplemented activity. Analysis of baseline tissue oxygen levels for the 3 measurement times showed no statistically significant effect for supplemented activity. Mean values (mm Hg [SD]) for the standard activity group were as follows: day 0: 57 (12), day 1: 50 (12), day 2: 41 (9); and for the supplemented activity group: day 0: 56 (8), day 1: 48 (8), day 2: 40 (9) ($F = 0.586, P = 0.48$). There was a significant effect of time for baseline oxygen ($F = 47, P < 0.00$), with a consistent daily decrease in oxygen levels, but no significant interaction of time and protocol.

Mean tissue oxygen levels (SD) in response to the 50% oxygen challenge were as follows: standard activity group day 0: 76 (24), day 1: 69 (34), day 2: 45 (12); supplemented activity group day 0: 69 (12), day 1: 62 (11), day 2: 44 (13). The groups did not differ significantly ($F = 1.7, P = -18$). There was a significant within-subject effect for time on tissue oxygen levels

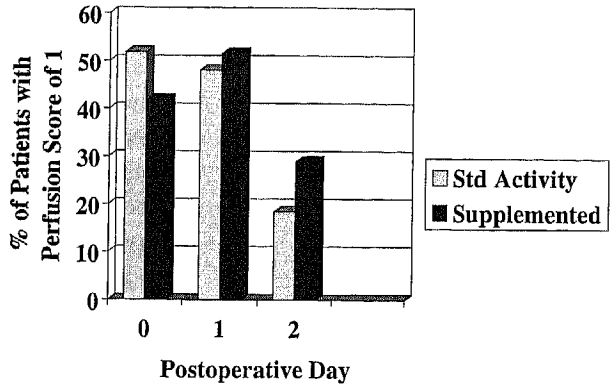

Figure 3. Percent of patients with positive perfusion scores in response to oxygen. Perfusion scores were either 0 (indicating < 20% increase in tissue oxygen in response to breathing supplemental oxygen) or 1 (indicating a 20% increase in tissue oxygen above baseline value).

(F = 33, P < 0.00), but no time interaction with protocol.

Perfusion

Chi-square analysis of perfusion scores for each day resulted in no significant differences between standard and supplemented activity groups: day 0: χ^2 = 0.17, P = 0.68; day 1: χ^2 = 0.27, P = 0.59; day 2: χ^2 = 1.4, P = 0.24. Figure 3 displays the percent of participants in each group with scores of 1, indicating a peripheral response to breathing oxygen and good peripheral perfusion. Slightly higher percentages of participants in the active group showed better perfusion, but this was not statistically significant.

Discussion

The purpose of this study was to investigate whether wound-healing responses and local perfusion and tissue oxygen levels close to the surgical THR wounds were improved by early and supplemented postoperative physical activity. Previous observations of increased wound strength in the presence of greater physical activity suggest a positive effect on connective-tissue formation or greater organization of collagen. Activity performed by patients having THR that participated in this study did not produce gains in wound-healing responses measured by collagen message or amount of protein in the ePTFE samples. The significantly higher level of DNA documented in the samples of the supplemented activity group suggests some increase in cellularity or cell activity. Participants in the active group had slightly higher, though nonsignificant, histology scores for FBs and MPs, indicating higher cell numbers in the samples and congruence with DNA results. As a whole, the wound response results indicate that activity in the early postoperative period does not offer significant benefit for subcutaneous tissue repair at the 1-week point after surgery. Given the single measure of this endpoint and the increased DNA, evaluation of wound response beyond 7 days might yield evidence of improved collagen deposition. This, however, was not possible to establish in this study. Although there are not other reports of subcutaneous tissue healing available for comparison, a similar lack of dramatic effect on cartilage repair has been reported in rats with articular cartilage defects that were treated with exercise following injury (Murrell and others 1998; Espanha and others 2001). However, it is also possible that a higher intensity of exercise might be needed to induce increases in matrix production and that the level of exercise in this study fell short of a level that might stimulate repair.

Increases in tissue oxygen were not observed with the early supplemented postoperative activity. However, the additional activity did not reduce tissue oxygen levels, which fell within acceptable parameters on the day of surgery and the 1st postoperative day for both groups. This early postsurgery period is believed to be critical for maintaining adequate tissue oxygen in healing tissues to prevent wound infection (Hopf and others 1997). On these 2 days, mean $PscO_2$ levels in both groups in response to breathing oxygen exceeded 60 mm Hg, whereas mean $PscO_2$ levels on the 2nd postoperative day fell below optimum levels in both groups. Other factors can reduce tissue oxygen response, including hypovolemia (Greif and others 2000), hypothermia (Kurz and others 1996), pain (Akca and others 1999), increased sympathetic response, or increased tissue edema. These factors were not controlled for and may have influenced any potential oxygen response related to activity. To reduce ambiguity in results, the design of future studies to evaluate how activity affects peripheral oxygen supply

should incorporate measures to correct low volume, maintain normothermia, and control pain.

The effect of low- to moderate-intensity activity on subcutaneous perfusion has received little study and is not well documented. The moderate level of postoperative physical activity performed in this study did not significantly improve peripheral subcutaneous perfusion above that found in control participants. Somewhat higher percentages of participants participating in the intervention had positive perfusion scores (59% vs. 52% day 1, 35% vs. 20% day 2), but differences were not significant. If increased activity is associated with improved perfusion, it is likely that a larger sample would be required to demonstrate an effect.

In regard to increased postoperative activity as an intervention, 80% of participants randomized to supplemented activity achieved 100% protocol adherence. Participants reported no adverse events or complaints related to the extra activity. This indicates the acceptability, feasibility, and safety of increasing postoperative activity. Although extra activity may not benefit wound healing, there are other associated benefits such as protection from deep vein embolism and thrombosis (Ragucci and others 2003) that provide reason to increase activity as soon as possible after surgery. In addition, upper-arm strength is needed after THR because walking is dependent on the use of devices to assist mobility (e.g., crutches or walker). Although this study failed to show wound-healing benefit of supplemented activity, results of a secondary analysis (Whitney and Parkman 2001) suggest that preoperative exercise may promote recovery of mobility after THR and that early, increased postoperative ambulation is associated with earlier discharge in THR patients. These results validate the value of physical activity for promotion of recovery generally and provide a basis for further studies on the role of activity in patients facing surgery.

Conclusion

Increases of tissue oxygen levels, perfusion, matrix production, and cellular markers of healing were not associated with the early, supplemented postoperative activity used in this study. Interestingly, the enhanced level of activity did not decrease tissue oxygen levels from those observed in the standard activity group. Nor was additional activity detrimental to matrix formation. The majority of intervention group participants adhered to the supplemented activity protocol and tolerated this level of activity well. Blood flow and oxygen response in peripheral tissues in clinical populations is complex and dependent on several factors that need to be considered in the design of future studies. The mechanisms of salutary effects of early ambulation are still not understood and require further exploration.

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