Journal of Investigative Surgery, 24, 257–261, 2011

ISSN: 0894-1939 print / 1521-0553 online
DOI: 10.3109/08941939.2011.589885

informa
healthcare

ORIGINAL RESEARCH

Platelet-Rich Plasma Application and Heterotopic Bone Formation Following Total Hip Arthroplasty

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ABSTRACT

Activated blood platelets play a critical, early role in the wound healing response by releasing several types of growth factors at the site of injury which mediate the initial stages of tissue repair. Autologously derived platelet-rich plasma has been applied during surgery as a healing aid and some studies have shown benefit with total joint arthroplasty procedures such as in the knee. However, little has been published regarding the use of platelet-rich plasma during total hip arthroplasty. The hip is especially prone to develop islands of heterotopic bone following arthroplasty which can lead to pain, limited motion, and even ankylosis of the joint. If this condition is exacerbated by platelet-rich plasma, this could present a barrier to the use of this adjuvant in total hip arthroplasty. This retrospective, controlled clinical study examined the effect of platelet rich plasma application during closure following total hip arthroplasty on heterotopic ossification. By one year, 21.3% of the control patients developed heterotopic bone (91 patients, 94 hips, Brooker grades I–III) compared to 12.9% of the treatment patients (76 patients, 85 hips, Brooker grades I–II). These differences were not significant ($p = 0.478$, power $= 0.90$). Thus, the use of platelet-rich plasma in this procedure does not appear to influence the incidence or severity of heterotopic ossification which should help to justify further clinical research to more fully understand whether this autologous blood product has a role in total hip arthroplasty.

Keywords: total hip arthroplasty, heterotopic bone, ossification, platelet-rich plasma, healing, PRP

INTRODUCTION

Heterotopic ossification (HO) is the formation of lamellar bone in soft tissue structures where bone does not normally exist [1]. HO formation about the hip is common following total hip arthroplasty (THA). The incidence is 2–90% [1–4], or about 43% overall [5]. Its severity can range from asymptomatic isolated islands of bone to bone bridging the femur and acetabulum resulting in hip ankylosis [6], with 3–10% of patients with HO after THA experiencing limitation of motion or painful impingement [4, 7]. While the etiology is unknown, several risk factors have been identified [1–4, 7–9]. The incidence can be minimized in high risk groups by postoperative radiotherapy or treatment using nonsteroidal antiinflammatory drugs (NSAIDs) [2, 4, 8, 10].

Wound healing is mediated by the spatial and temporal distribution of signaling proteins elicited in the local response to tissue injury [11]. Activated blood platelets produce rapid hemostasis and initiate growth factor and cytokine release. Investigators have examined the application of autologous platelet-rich plasma (PRP) to the surgical site in a variety of surgical procedures in an effort to improve outcomes [11, 12]. Some of the signaling proteins elicited by platelets may promote HO [7, 13, 14] which could limit its usefulness in THA. To date, no studies have examined this [11, 12, 15, 16]. The purpose of this study was to investigate the influence of PRP on HO following THA by retrospective comparison of treatment (with PRP) and control THA patient cohorts.

MATERIALS AND METHODS

This was a retrospective, controlled, IRB-approved clinical study with data obtained through chart review.

Received 31 March 2010; accepted 17 May 2010.

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One hundred seventy nine sequential primary hip arthroplasties were performed in 167 patients during 1999–2006 for which follow-up radiographs were available. Femoral components used were the Taperloc® or the Mallory/Head® stems (Biomet, Inc., Warsaw, IN, USA) utilizing metal on metal, or metal on polyethylene, articulation. Stems were either press fit or cemented. Acetabular shells were all press fit. The inclusion criteria were patients with full skeletal maturity undergoing primary THA. Exclusion criteria included patients undergoing revision THA; previous fracture and open reduction in the same hip; a history of spinal trauma and head injury, encephalitis, meningitis, myelitis, tetanus, tumors, epidural abscess, and genetic disorders (fibrodysplasia ossificans progressive, progressive osseous heteroplasia, and Albright's hereditary osteodystrophy). NSAIDs were stopped two weeks before the procedure and were not routinely prescribed postoperatively. The hips were implanted using a posterior lateral approach.

The study population was divided into two groups—those receiving PRP (treatment group, 76 patients, 85 hips, performed January, 2004 to February, 2006) and those that did not receive this adjuvant (control group, 91 patients, 94 hips, performed March, 1999 to December, 2003). The Gravitational Platelet Separation system (GPS® system, Biomet Biologics, Warsaw, IN, USA) was used to prepare the PRP, and has been previously described [17]. Briefly, 55 ml of venous blood was drawn from the patient 30 min before surgery into a 60 ml syringe that contained 5 ml of acid-citrate-dextrose-A (ACD-A) anticoagulant. The anticoagulated blood was transferred into the GPS® tube and was centrifuged at 3,200 RPMs for 15 min. This permitted the blood to stratify into three layers (from top to bottom): platelet poor plasma (PPP), buffy coat, and packed red cells. The buffy coat, which contained the platelets, was sequestered in a small compartment that also contained 6 ml of PPP. The tube was vigorously shaken for 30 s to suspend the buffy coat, creating approximately 6 ml of PRP. The PRP was withdrawn from the tube into a 10 ml syringe. The activation solution was prepared by mixing 1,000 units of topical bovine thrombin per ml of 10% calcium chloride solution. Activation solution was drawn into a 1 ml syringe. The PRP syringe and the activation syringe were connected in tandem to a dual sprayer apparatus. This enabled the two syringes to form a combined spray in the volumetric ratio of 10:1, respectively. In this manner, the PRP became activated during its transit to the wound site. During closure in the treatment patients, the activated PRP was sprayed onto the exposed bone, any bone graft present, synovium, capsule, and muscle. Postoperative drains were not placed in the hips.

Routinely, radiographs (anterior–posterior and lateral) were performed four times: immediate post-op, six weeks, three months, and one year. Based on the radiographic examination, HO was graded per the Brooker classification [6]. Other data collected included gender, age, principal diagnosis, operative side, and previous contralateral surgery. Continuous variables between the two groups of patients were compared using the two-tailed Student *t*-test. Proportional data were compared using the chi-square test. Significance was taken for values of p less than .05.

TABLE 1 Patient demographics

	Control	Treatment	*p*-value
No. patients	91	76	N/A
No. hips	94	85	N/A
Bilateral/unilateral patients	3/88	9/67	.067
Male/female ratio	48/43	34/42	.381
No. right side	55/94	39/85	.124
Age (ave±SD, range)	71.6 ± 9.9, 22–92	68.4 ± 14.3, 48–91	.081
Principal diagnosis OA[a]	91/91	82/85[b]	.210
No. with previous contralateral hip surgery	28/94	26/85	.963

[a]Osteoarthritis.
[b]Three hips did not have primary diagnosis data and were assumed to be other than OA as a worst case.

RESULTS

Table 1 summarizes the patient demographics. As can be seen, both populations were comparable. Table 2 summarizes the results of heterotopic bone formation. Figure 1 shows a radiograph of Brooker Grade III HO in a control hip for illustration. Not all patients had follow-up radiographs at the earlier intervals, but all had radiographs at one year. Hence, cited results correspond to the one-year radiographs. There were a total of 20 (21.3%) control hips and 11 (12.9%) PRP-treated hips that exhibited heterotopic bone. In the case of the control hips, these were distributed among grades I–III while in the case of the PRP-treated hips, these were limited to grades I and II. None of these differences were significant ($p = 0.478$). The power of this study was calculated using the actual difference in the proportions of hips exhibiting HO between the two groups, i.e., a noninferiority margin of 8.4%, and the actual sizes of the treatment and control groups, i.e., 85

TABLE 2 Brooker grade of heterotopic bone formation

	Brooker grade of heterotopic bone formation in hip				
Group	0	I	II	III	IV
Control	74 (78.7%)	11 (11.7%)	7 (7.4%)	2 (2.1%)	0
Treatment	74 (87.1%)	7 (8.2%)	4 (4.7%)	0	0

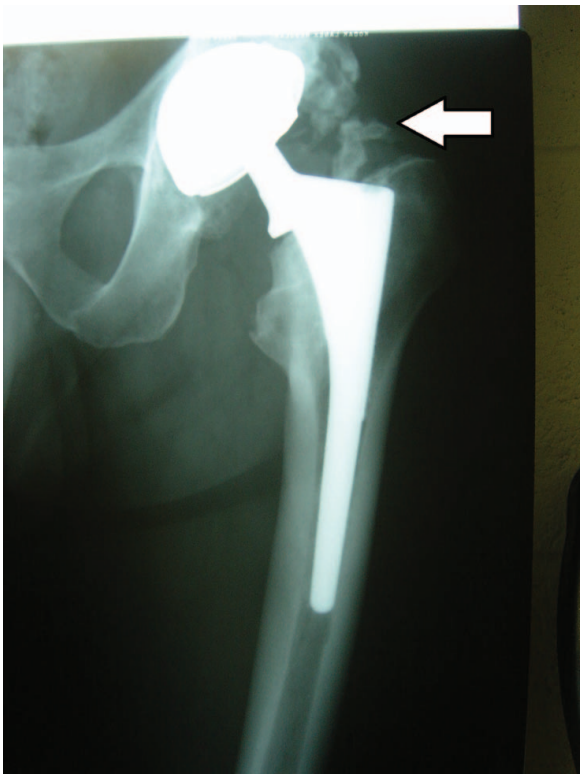

FIGURE 1 Control hip (no PRP) showing Brooker Grade III heterotopic bone (see arrow).

hips and 94 hips, respectively. As such, the power of the two group chi-square test of equivalance in proportions was 90%.

DISCUSSION

HO is the most common complication of THA, with the exact cause and pathogenesis unknown [1, 3]. It is typically asymptomatic and detected only as an incidental finding on a radiograph [12]. When it occurs it is usually apparent within four to six weeks after injury, with bone maturation progressing between three and six months [1, 2, 4, 13]. After six months, HO rarely increases [2, 18]. As such, one-year follow-up was sufficient to measure the incidence of HO. Although the study cohort had a lower incidence of HO than the control cohort (12.9% vs. 21.2%), this difference was not significant. Also, the distribution of HO grade was similar in both with no instances of the most severe grade IV.

Although several risk factors have been identified that predispose THA patients to HO including male gender, age >65 years, obesity, inexperience of the surgeon, surgical approach, type of implant, and others [1–4, 7–9, 14, 18–20], most patients that develop HO have no identifiable risk factors [21].

The etiology of HO is uncertain, but is believed to be multifactorial [14]. McCarthy [7] states that four factors are necessary for its formation: (1) an inciting event, typically trauma, which results in a hematoma, (2) a signal from the site of the injury, (3) a supply of mesenchymal cells which, given an appropriate signal, can differentiate into osteoblasts and chondroblasts, and (4) an appropriate environment conducive to the continued production of heterotopic bone. Interestingly, for HO to form in the hip or knee, the injury does not have to be local to the site but can include spinal injury and head trauma, suggesting the influence of systemic factors [1, 2, 10]. The reaming performed during THA spreads bone marrow into the muscles [2]. Thus, osteogenically competent progenitor cells are exposed to well-vascularized muscle. Osteoinductive factors and growth factors released from the traumatized tissue, especially the bone, may induce these cells into an osteogenic pathway.

Platelets naturally accumulate in a large number at the site of tissue injury [11]. During activation, they become sticky and form a platelet plug, providing hemostasis. Activation also causes the alpha-granules to fuse with the platelet membrane and extracellularly release numerous signalling proteins. These proteins, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), and others, positively influence many aspects of healing [11, 22]. This forms the theoretical basis for using PRP to deliver a supraphysiological dose of platelets in anticipation of accelerated wound repair.

The literature is equivocal on whether use of PRP during THA would be expected to increase, decrease, or not affect HO. First, many of the commercial systems used to intraoperatively prepare autologous PRP differ in their ability to concentrate platelets and growth factors which can affect clinical results [11, 12]. Second, it is important that platelets remain intact and unactivated during PRP preparation to maximize the recovery of bioactive secretory proteins [11, 23]. Available systems may differ in their ability to maintain platelet integrity which can effect outcomes. Third, the effect of PRP on HO may depend on the state of PRP activation during delivery [24, 25]. Fourth, there is a paucity of randomized, controlled clinical studies that confirm whether PRP actually promotes soft and hard tissue healing [11, 12]. Fifth, PRP is not inherently osteoinductive [24]; however, BMP-2 and BMP-4 have been identified within platelet lysate [26] which suggests that they might contribute to bone formation and repair. Collectively, these points illustrate the complexity of the effects of PRP in hard and soft tissue healing. Coupled with the uncertainty over the basic mechanism of HO following THA, casting the potential influence of PRP on the process in a theoretical context is difficult.

The basic steps of wound healing are similar for both soft tissue and bone, including three overlapping phases–inflammatory, proliferative, and

remodeling [11]. During the proliferative phase, the damaged, necrotic tissue is replaced with living tissue that is specific to the local tissue environment (hard or soft) [11]. Local factors, including the growth factor and cytokine profile, hormones, nutrients, pH, oxygen tension, and the electrical and mechanical environment, mediate the differentiation of mesenchymal stem cells (MSCs) into osteoblasts, fibroblasts, chondrocytes, and other cell types as required to generate the appropriate type of tissue. Although reaming during THA spreads bone marrow into the surrounding soft tissue, it may be that the local environment remains sufficiently "soft tissue-like" to preclude PRP from directing additional HO bone to form.

There were some limitations to this study. First, while all patients had a one-year follow-up radiograph, not all had six-week and three-month exams. As such, whether PRP influenced the time of onset of HO could not be determined with certainty although there did not appear to be any overt difference in this regard between the two cohorts (data not shown). Second, being overweight is a positive influence on HO in the hip [18, 20], yet body mass index (BMI) data were unavailable for our patients. However, it is unlikely that there was a significant difference in BMI between the control and treatment cohorts in our study. Third, there are many outcomes that PRP could potentially influence that were not examined here. These include blood transfusion requirements, wound drainage, infection, pain, and range of motion. Thus, this study did not provide evidence that PRP should be used in THA surgery, but rather, provided evidence that its use does not appear to increase the incidence and severity of the most common complication.

Specialized equipment is required to prepare PRP and there are costs involved through the use of disposables and technician time. There is also a minor risk to the patient to the venous blood draw and to the use of bovine thrombin [27, 28]. As such, the decision on whether to use PRP or not should not be based on intuition or what seems to "make sense," but rather, on sound scientific data. Berghoff, et al. [17] performed a retrospective study on total knee arthroplasty patients based on whether the patients received PRP and PPP during wound closure. The use of these autologous blood products was associated with a significant reduction in hospital stay and blood transfusion use, improved hemoglobin profile for the first two postoperative days, and improved ROM through six weeks. Although this suggests that similar benefits might be achieved in THA patients, this remains to be proven. Future studies should be controlled, be randomized, and utilize several outcome measures to establish whether there is a clinical benefit to the use of PRP in THA surgery. That PRP application did not increase the incidence or severity of HO helps to justify continued clinical investigation.

CONCLUSION

The use of autologous PRP during closure following THA does not appear to affect the incidence or severity of HO about the hip. As such, this study provided evidence that this potential barrier to its use for this procedure may not exist. Nevertheless, future work will be required to establish whether there is a true clinical benefit for using this autologous blood product during hip joint replacement.

ACKNOWLEDGMENTS

The authors would like to thank Andrés Mauricio Monasterios, M.D. and Ramón Vallenilla, M.D. for their work in reviewing patient charts and extracting data.

Declaration of Interest: The first author is a paid consultant of Biomet, Inc., and the second author is an employee of Biomet, Inc. Biomet, Inc. provided funding for this study.

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