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Original research

Are reinfusion drains safe to use with periarticular liposomal bupivacaine? An analysis of systemic bupivacaine toxicity

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ABSTRACT

Background: Intraoperative periarticular injection (PAI) with local anesthetic is an important component of multimodal pain control in total joint arthroplasty (TJA). A potential risk of this practice is serum anesthetic toxicity resulting from the autotransfusion of blood collected from a reinfusion drain. The purpose of this study is to evaluate the levels of bupivacaine in blood collected in an autotransfusion system after use of a PAI in TJA.

Methods: In this prospective study, each TJA patient had an identical PAI consisting of 20 cc of liposomal bupivacaine, 30 cc of 0.25% bupivacaine with epinephrine, and 10 cc of normal saline. An autologous reinfusion drain was utilized in all patients. At 2 and 5 hours postoperatively, blood was collected from the autotransfusion canister and sent to the laboratory to quantify bupivacaine levels. The sums of these levels were compared to the lowest reported serum bupivacaine dose associated with toxicity (1.1 mg/kg).

Results: Eleven unilateral TJA patients were enrolled (6 total knee arthroplasties, 5 total hip arthroplasties). The average 2-hour serum bupivacaine level was 2.9 μg (range 0.8-5.6) while the average 5-hour serum bupivacaine level was 4.5 μg (range 0.4-10.0). The average sum of the 2-hour and 5-hour serum bupivacaine level was 5.6 μg (range 0.8-13.6). Each of the 11 patient samples were well below their minimum serum bupivacaine dose toxicity.

Conclusions: Use of a reinfusion drain after PAI with liposomal bupivacaine in TJA appears safe, as bupivacaine levels in the autotransfused blood remains well below the reported minimum serum toxic dose.

Level of Evidence: IV.

Introduction

Perioperative pain control is a major concern of both patients and surgeons in total joint arthroplasty (TJA) [1]. Suboptimal pain control in the postoperative setting can compromise patient satisfaction and outcomes [2]. Narcotic pain medication has been the major component of postoperative pain control for decades [3-5]. However, as narcotic use is associated with increased cardiac, respiratory, and neurologic complications, there has been a move toward non-narcotic modalities including central and regional anesthesia, nonsteroidal pain medication, and periarticular injections (PAIs) [6,7].

PAIs involve intraoperative, periarticular soft tissue infiltrations of local anesthetics during TJA procedures [8]. These injections have been shown to lower postoperative visual analog scores and narcotic usage, while avoiding the risks of nerve blocks and demonstrating higher satisfaction scores and earlier times to rehabilitation milestones [2,9-14]. Use of longer acting anesthetics, such as ropivacaine or bupivacaine, in combination with other pain

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management modalities mitigate concerns surrounding early rebound pain with its use as a monotherapy [2,11,15].

TJA can result in a sizeable blood loss, often resulting in a considerable postoperative decline in hemoglobin [16]. Allogeneic blood transfusions (ABTs) are frequently required in these situations; however, patients who require ABTs often experience longer hospital stays, higher cost of care, and increased medical and surgical complications [17]. With these issues in mind, a number of historical (preoperative autologous donation) and innovative strategies (reinfusion drains and tranexamic acid) in blood management have been reported in recent years. In the modern era of tranexamic acid and restrictive blood transfusion practices, the rate of allogenic blood transfusion had been reduced dramatically and the role of reinfusion drains had diminished. However, in certain situations, such as patients with chronic anemia or opposition to receive allogeneic blood, the use autologous reinfusion drains may play an important role. In addition, some studies have demonstrated their ability to decrease the need for ABT after TJA [18].

While trying to optimize patient outcomes and satisfaction with new pain management modalities such as PAIs, combined with decreasing risk associated with ABTs in perioperative blood management, the question arises whether the autotransfusion of shed blood is safe following TJA in which a PAI with liposomal bupivacaine was utilized. Parker et al and Breindahl et al answered this question by measuring the shed blood and plasma concentrations of local anesthetic. Both studies demonstrated that measured levels of local anesthetic did not reach toxic thresholds [19,20]. Liposomal bupivacaine (LB) (Exparel; Pacira Pharmaceutical Inc., Parsippany, NJ) became available in the United States in 2003. LB is an extended-release formulation of lipid-encapsulated bupivacaine designed for a controlled release of up to 72 hours [21,22]. This has made it appealing to surgeons for use in PAIs in TJA [10,23,24]. Unlike plain local anesthesia, such as ropivacaine or levobupivacaine, a gap in the literature exists regarding the levels of LB in shed blood in reinfusion systems after PAI in TJA. The purpose of this study is to evaluate the levels of serum bupivacaine within the blood collected by an autologous reinfusion system following TJA in which a PAI with LB was utilized.

Material and methods

Following study approval from a local institutional review board and an informed consenting process, 11 consecutive TJA patients were prospectively enrolled. The study was carried out by a fellowship-trained, TJA surgeon (B.D.S.). Inclusion criteria were patients over the age of 18 undergoing a primary, unilateral total hip arthroplasty (THA) or total knee arthroplasty (TKA) for end-stage osteoarthritis. Exclusion criteria included a diagnosis other than osteoarthritis or an allergy to local anesthetic. Six of the patients enrolled underwent a TKA. Five patients underwent a THA. Patient demographics such as age, gender, height, and weight were recorded.

Each TKA was performed via a standard anterior midline skin incision and a medial parapatellar arthrotomy. A cemented posterior-stabilized prosthesis with patellar resurfacing (Triathlon; Stryker, Kalamazoo, MI) was utilized in all cases. In addition to a pneumatic thigh tourniquet, all cases underwent identical intraoperative PAIs consisting of 20 cc of LB (Exparel; Pacira), 30 cc of 0.25% bupivacaine with epinephrine, and 10 cc of normal saline (60 cc total). This was identically and systematically injected into the posterior capsule, periosteum of the medial and lateral femoral condyles, exposed quadriceps musculature, and capsule. The injection followed the company's (Pacira) recommended infiltration practice for TKA with a 22 g needle. Prior to closure, all TKA patients underwent placement of a subfascial autologous reinfusion drain (OrthoPat; Haemonetics Corporation, Braintree, MA). None of the total knee patients required a blood transfusion postoperatively. Aspirin was utilized for venous thromboembolism prevention.

Each THA was performed via a standard posterolateral skin incision and a gluteus maximus muscle-splitting approach. The external rotators and posterior capsule were sharply excised off the greater trochanter and dorsal proximal femur. Cementless, press-fit acetabular and femoral components were utilized in all cases (Corail; DePuy Synthes, Warsaw, IN). After placement of the prostheses and repair of the external rotator-capsular complex, each patient received an identical and systematically allocated PAI placed along the posterior and anterior capsules: vastus lateralis, gluteus medius, and gluteus maximus musculature, and iliotibial band. The injection consisted of 20 cc of LB (Exparel; Pacira), 30 cc of 0.25% bupivacaine with epinephrine, and 10 cc of normal saline (60 cc total). The injection followed the company's (Pacira) recommended infiltration practice for THA with a 22 g needle. Prior to closure of the iliotibial band, all THA patients received an autologous reinfusion drain (OrthoPat, Haemonetics Corporation). None of the total hip patients required a blood transfusion postoperatively. Aspirin was utilized for venous thromboembolism prevention.

At 2 and 5 hours following the conclusion of the case, 4 cc of blood samples were collected from the autotransfusion filtration canister and sent to the laboratory to quantify bupivacaine levels. Patient #6 and #8 did not have enough blood in the autotransfusion canister at 2 hours to collect 4 cc of blood samples. Patient #9 to #11 did not have enough blood at the 5-hour mark in order to collect samples. Additional blood in the canister was discarded. To mitigate inconsistent drain outputs at the 2-hour and 5-hour marks, the sums of the concentrations for each patient were compared to the lowest reported cardiovascular (CV) toxic threshold for intravenous bupivacaine in the literature of 1.1 mg/kg [25]. Weight-based minimum thresholds were calculated. We then multiplied this minimum toxic threshold for CV toxicity by the inverse of the sum of the 2-hour and 5-hour bupivacaine concentrations in blood samples from the study patients' autotransfusion canisters (Table 1). This calculation yielded the amount of blood needed to be autotransfused given the found bupivacaine concentrations to breach the lowest reported threshold for CV toxicity.

A similar calculation was carried out to compare the lowest reported minimum bupivacaine threshold for central nervous system (CNS) toxicity (300 μg/L) [27]. As this threshold is reported as a concentration, we calculated the estimated blood volume (EBV) for each patient using Nadler's formula that comprised gender, height, and weight (Table 1) [26]. We multiplied the EBV and the lowest reported threshold for CNS toxicity (300 μg/L) for each patient to obtain the amount of micrograms of bupivacaine that would cause CNS toxicity. We then multiplied this minimum toxic threshold by the inverse of the sum of the 2-hour and 5-hour bupivacaine concentrations in blood samples from the study patients' autotransfusion canisters (Table 1). This calculation yielded the amount of blood needed to be autotransfused given the found bupivacaine concentrations to breach the lowest reported threshold for CNS toxicity.

Table 1
Equations used for calculations.

Estimated blood volume [26]	Male: 0.3669 × Height in m^3 + 0.03219 × Weight in kg + 0.6041 Female: 0.3561 × Height in m^3 + 0.03308 × Weight in kg + 0.1833
Cardiovascular toxicity	$(2 + 5\ h\ \mu g/cc)^{-1}$ × 1100 μg/kg × Weight in kg
Central nervous system toxicity	300 μg/L × EBV (L)

Because we were unaware of the potential bupivacaine levels in the collected blood prior to conducting this study, no blood was ever autotransfused back to patients in this study. After the 5-hour sample, the drain was then attached to a low, continuous-suction hemovac. The drains were promptly removed in the morning hours of postoperative day 1. Any complications that surround the procedure and drain management were recorded.

Results

Eleven patients were enrolled. There was no attrition from the study. Six patients underwent TKA, while 5 patients underwent THA. Demographic data including procedure, age, gender, height, weight, and EBV are summarized in Table 2. There were no intraoperative complications associated with the procedures or postoperative adverse events associated with drain management. None of the patients developed a periprosthetic joint infection or wound complication in the acute postoperative period.

There was insufficient output in the autotransfusion canister in 2 patients at 2 hours and in 3 patients at 5 hours postoperatively to collect and send 4 cc of blood samples to the laboratory. Using the lowest toxic intravenous bupivacaine level reported in the literature (1100 μg/kg), the minimum cardiotoxic level was calculated for each patient based on each individual's weight (kg) (Table 3) [25]. For a mean weight of 99.3 kg, the mean minimum toxic bupivacaine level was 109,270 μg of bupivacaine. The 2-hour and 5-hour bupivacaine levels measured from blood obtained from the autotransfusion canister are listed for each patient in Table 4. The mean 2-hour bupivacaine level was 2.9 μg. The mean 5-hour bupivacaine level was 4.35 μg. The mean sum of the 2-hour and 5-hour bupivacaine concentrations was 0.91. The average amount of blood that needed to be autotransfused to produce symptoms of CV toxicity was over 120 L (Table 3).

Each patient's EBV was based on Nadler's formula utilizing gender, height, and weight (Tables 1 and 2) [26]. Using this EBV, individual minimum bupivacaine level thresholds for CNS toxicity was calculated based on the minimum threshold reported by Knudsen et al (0.3 mg/L) (Table 1) [27]. The mean bupivacaine threshold for CNS toxicity was 1668 μg. Table 5 further summarizes each individual's minimum bupivacaine level threshold for CNS toxicity. The median amount of autotransfused blood needed to produce CNS symptoms of toxicity was 2103 cc. The minimum amount of blood needed to produce CNS symptoms was 721.4 cc.

Discussion

Perioperative pain management and blood conservation in TJA have continued to evolve over the last few decades. With the goals of decreasing opioid dependence and optimizing patient satisfaction, PAIs with long-acting anesthetic have been introduced in order to decrease opioid consumption, postoperative pain scores, and length of stay.

Similar to perioperative pain control, perioperative blood conservation has continued to evolve. From autologous preoperative donation to autologous reinfusion drains to tranexamic acid, new innovations in perioperative blood management continue to be introduced. Autologous reinfusion drains were introduced in order to reduce the need for allogeneic transfusion and remain an option to limit ABT risk [28]. Since autologous reinfusion drains were first introduced in the 1990s, concerns regarding transfusion of shed blood following a PAI with local anesthetic have been voiced [19]. High levels of serum bupivacaine have been associated with both CNS and CV system side effect, with CNS effects usually occurring before CV symptoms. These CNS symptoms can include numbness of the tongue, lightheadedness, visual disturbances, and fasciculations [25]. From a CV perspective, the most severe effects from toxic doses can include CV depression that may lead to cardiotoxicity and eventual death [27].

Several published reports have demonstrated that plain local anesthetic shed into the prosthetic hip or knee joint following replacement does not lead to toxic serum levels following autotransfusion [19,20,29,30]. Parker et al [19] initially investigated this in 20 patients undergoing TKA who underwent autotransfusion of blood following PAI with ropivacaine. The authors found that peak serum levels following autotransfusion were well below toxic thresholds. Gill et al quantified drain serum levels of ropivacaine following TKAs in which a PAI was utilized. The authors found that the concentration of ropivacaine in the shed blood was 6-fold lower than the reported toxic threshold. Breindahl et al [20] assessed

Table 2
Patient demographics.

Patient	Procedure	Gender	Age (y)	Height (inches)	Weight (kg)	EBV (L)
Patient 1	THA	Male	67.2	70	102.3	5.97
Patient 2	THA	Female	80.3	61	79.8	4.15
Patient 3	THA	Female	63.8	63	69.4	3.94
Patient 4	TKA	Male	63.6	76	138.4	7.71
Patient 5	TKA	Male	73.4	68	94.3	5.54
Patient 6	THA	Male	67.3	66	91.6	5.29
Patient 7	TKA	Male	79.0	71	91.9	5.30
Patient 8	TKA	Female	55.6	70	95.7	5.36
Patient 9	TKA	Male	63.2	72	125.2	6.89
Patient 10	THA	Female	47.0	68	88.9	4.97
Patient 11	TKA	Male	57.2	66	115.2	6.05

Table 3
Cardiovascular toxicity.

Patient	CV toxicity threshold (μg)	Blood volume needed for toxicity (cc)
Patient 1	112,530	750,200
Patient 2	87,780	585,200
Patient 3	76,340	95,425
Patient 4	152,240	138,400
Patient 5	103,730	47,150
Patient 6	100,760	45,800
Patient 7	101,090	59,464
Patient 8	105,720	526,350
Patient 9	137,720	229,533
Patient 10	97,790	69,850
Patient 11	126,720	316,800
Mean	109.720	120,076

Table 4
Two-hour, 5-hour, and 2 + 5-hour bupivacaine concentrations.

Patient	2-h Bup level (μg/cc)	5-h Bup level (μg/cc)	2 + 5-h Bup level (μg/cc)
Patient 1	0.2	0.1	0.15
Patient 2	0.1	0.2	0.15
Patient 3	1.3	0.3	0.8
Patient 4	0.6	1.6	1.1
Patient 5	1.1	1.6	1.32
Patient 6	NA	2.2	2.2
Patient 7	0.9	2.5	1.7
Patient 8	NA	0.2	0.2
Patient 9	0.6	NA	0.6
Patient 10	1.4	NA	1.4
Patient 11	o.4	NA	0.4
Mean			0.91

NA, not applicable.

Table 5
Central nervous system toxicity.

Patient	CNS toxicity threshold (μg)	Blood volume needed for toxicity (cc)
Patient 1	1791	11,940
Patient 2	1245	8300
Patient 3	1182	1477.5
Patient 4	2313	2102.7
Patient 5	1662	1259.1
Patient 6	1587	721.4
Patient 7	1590	935.5
Patient 8	1608	8040
Patient 9	2067	3445
Patient 10	1491	1065
Patient 11	1815	4537.5
Mean	1668	3984

serum levels of ropivacaine following PAIs in 25 TKAs and 27 THAs. While they demonstrated a significant increase in serum concentration of total ropivacaine for TKAs, all patients remained under the threshold for ropivacaine toxicity [27]. We also utilized the threshold of 300 μg/L reported by Knudsen et al for CNS toxicity from intravenous bupivacaine.

Only one other study to date assessed bupivacaine, specifically levobupivacaine, and its potential toxicity after autotransfusion of blood following TJA with PAI [30]. Levobupivacaine is an enatomer of bupivacaine that is reported to be less toxic and long lasting [31]. Wallace et al [30] found that patients who received a PAI during TKA did not have clinically relevant levels of levobupivacaine in their blood.

Our study is the first to specifically assess LB (Exparel) for serum toxicity after autotransfusion of shed blood following PAI during TJA. Nevertheless, the results are consistent with other studies in the literature that have demonstrated that autotransfusion from reinfusion drains is safe after PAIs. All the patients in our study were well below the bupivacaine toxicity threshold for the CV system. However, the margin was smaller for drain serum bupivacaine levels and CNS toxicity thresholds. Based on our results, a range of 721-11,940 mL of blood would need to be transfused for the concentrations of bupivacaine to breach the lowest reported CNS toxic threshold of 300 μg/L by Knudesn et al based on patient's height and weight bupivacaine reinfusion drains concentrations become even less clinically relevant when considering that most THAs and TKAs do not produce enough posteroperative blood loss to allow autotransfusion of such significant amounts. However, it should be emphasized that a reinfusion amount of >700 cc is possible and practitioners should be aware of this possibility.

Sehat et al [16] recently published a study examining the blood loss following TJA with autotransfusion drains. The authors reported a mean drainage of 1039 mL from 101 THAs, with 388 mL of that amount reinfused. For TKAs, they reported a mean total drainage of 733 cc, with 388 cc reinfused [16]. While these authors utilized a different reinfusion system than we did, it appears that both reinfusion systems filter and wash the blood, resulting in only a fraction of the total drainage amount to be reinfused. Based on the results of our study, it appears that autotransfusion of drained blood following TJA using locally infiltrated LB is safe. However, one should be aware of the lower amount of blood autotransfused needed to produce neurotoxicity was 721 mL. Practitioners should be aware of this when high volumes of autotransfused blood are collected.

We acknowledge several limitations of this study. Foremost, the small number of patients enrolled in this prospective study and combining 2 different procedures (THA and TKA) limit any significant statistical analysis of the data and overall interpretation of the results Nevertheless, this study is a prospective, observational study assessing concentrations of bupivacaine and comparing it to historical toxic thresholds. Second, the missing data points for the 2-hour and 5-hour blood sample collections. We were unable to collect samples at these times as there was not enough blood in the reinfusion canister. To correct for this missing points, we utilized the sum of 2-hour and 5-hour samples to form a true concentration. Moreover, using the sum of the drained blood samples is more clinically relevant as most reinfusion systems call for one autologous reinfusion of drained blood after 5 or 6 hours of collection.

Conclusions

PAIs with local anesthetics, such as LB, are popular choices among surgeons for optimizing postoperative pain control. Furthermore, autologous reinfusion drains may be used to diminish the risk of allogenic blood transfusion following TJA. The bupivacaine concentrations in the drained blood in our study remained well below the lowest reported toxic thresholds for the CV toxicity and reinfusion amounts in excess of 700 mL would be needed to create CNS symptoms.

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