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Pain Management Strategies in Hand Surgery.

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PAIN MANAGEMENT STATEGIES IN AMBULATORY HAND SURGERY

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Synopsis

Modern anesthetic agents have allowed for the rapid expansion of ambulatory surgery and the continuously growing list of hand procedures performed in this setting. Nonetheless, adequate postoperative pain control remains a challenging problem for patients and surgeons alike. In this article we review various strategy options currently employed to attain pain control for patients undergoing ambulatory hand procedures.

An effective post-operative analgesic strategy begins with intraoperative anesthesia since it has been shown this can affect the level and perception of pain after surgery. The choice of general anesthesia, peripheral regional block with moderate sedation or bier block with its recent resurface with the use of a more distal tourniquet placement and less anesthetic, and the most newly described wide-awake surgery that is becoming more popular, depends on patient characteristics, coexisting conditions, location and expected length of the specific procedure. Once the patient is on the PACU, the combination of intravenous and oral medication can dictate the length of stay in the hospital as well as the level of pain control achieved in the first hours after sedation wears off. However, maybe the most challenging component of the analgesic strategy is the selection of the right home medication regiment as overmedication can lead to significant side-effects such as nausea, vomiting, sedation, dizziness, respiratory depression and substance dependence significantly affecting patients function, whereas inadequate pain control increases patient morbidity and suffering and results in repeat emergency room visits and calls to the office. There are many categories of medications to choose from including mild analgesics such as acetaminophen, NSAID's and the newer categories such as COX-2 selective inhibitors and ketorolac, as well as opioids and combinations thereof. Active exploration of new categories with a focus on extended, complete and safe pain relief with minimal effort from the patient has led to more modern strategies such as Continuous Peripheral Nerve Blockade (CPNB) and innovative formulations that pack established anesthetic agents in extended release biocompatible vehicles such as Exparel that can provide effective analgesia for over 96 hours. These modern strategies, even though are in just their early stages have generated some

very promising results and hold great promise in shaping the future of ambulatory hand surgery.

Keywords: Ambulatory Hand Surgery, Wide awake surgery, Combination analgesics, Nerve Block, Exparil

Key Points (5):

- The choice of intra-operative anesthesia and medication regiment in the PACU can have a great effect on hospital length of stay and recovery profile
- Wide awake surgery can be used for 95% of hand procedures and circumvents the need for preoperative testing while decreasing need for narcotics
- Newer Bier block modifications that include more distal tourniquet placement, allow for the use of less anesthetic making it a safer technique
- There is a shift away from opioid analgesic montherapies to combination formulations with complimentary mechanisms that can achieve greater efficacy and safety profile
- Exparil that s only approved for wound infiltration and can achieve 96 hours of analgesia is currently being investigated as a peripheral nerve block agent

INTRODUCTION

The exponential growth in medical technology and availability of better anesthetic agents, triggered a dramatic growth in ambulatory surgery over the last two decades. The rapid onset and termination of effect of modern anesthetic agents as well as better understanding of their mechanism of action, allowed longer cases to be performed on an ambulatory basis with quicker recovery of patients that can be discharged home more safely [1]. As of 2003, 70% of the surgical procedures in North America were performed on ambulatory basis and it now accounts for the majority

of surgery performed in USA, some European countries and Australia [1,2]. Orthopaedic, and more particularly hand procedures, account for a large portion of these outpatient surgeries [3] and are likely only to increase with time as healthcare economic restrictions continue to influence the way we practice. Leblanc et al [4] analyzed the cost and efficiency associated with performing carpal tunnel releases (CTR) in the main operating room as compared to the ambulatory setting and found that the use of the main OR for CTR is almost four times as expensive, and less than half as efficient as when performed in an ambulatory setting.

Even though expense and efficiency are important driving factors, perhaps the main prerequisite for performing ambulatory surgery is minimal postoperative pain that can be controlled with oral analgesics. With the ever-expanding boarders of what can be done as outpatient, pain control is something that still remains challenging for surgeons and patients alike [5]. It is estimated that up to 30–40% of ambulatory surgical patients suffer from moderate to severe pain during the first 24–48 hours after their discharge [2], which often times will interfere with sleep and daily functioning. Even though this improves with time, postoperative pain remains the most common reason for recurrent general practitioner office visits and unanticipated hospital admission [6-8]. This becomes especially important in hand patients. Chung et al [3] prospectively studied 1008 consecutive ambulatory surgical patients across 8 surgical specialties and found that in the PACU, orthopedic patients (that included hand procedures) had the highest incidence of pain, more so than urologic, general surgery and plastic surgery patients. Furthermore, in a survey by Rawal et al [7] that analyzed post-operative pain it was found that 37% of hand

surgery patients will suffer from moderate to severe pain post-operatively, affecting their function and quality of life.

Traditionally the patient's pain is managed with general anesthesia and narcotic medication for surgery, followed by oral medications, including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioid-containing oral analgesics (e.g., codeine-acetaminophen), or a combination of these along with intravenous pain medications (including patient-controlled analgesia), after surgery [9]. Despite the availability of these analgesic drugs, many patients still do not achieve effective pain control [10], often times because adverse gastrointestinal, hemostatic, and renal effects that become prohibitive to achieving adequate analgesic concentrations.

INTRA-OPERATIVE ANALGESIA/ ANESTHESIA

The choice of analgesia and anesthesia during the surgical procedure can have a great effect on the pain level and chance of successful pain control post-operatively and often dictates the length of stay of the patient in the hospital after the procedure.

General anesthesia

It has been known in the shoulder literature for quite some time [11] [12], that regional, as opposed to general anesthesia can result in shorter recovery times and faster hospital discharge after surgery. Similarly, Chan et al [13] prospectively examined three anesthetic techniques during hand procedures, namely general anesthesia (GA) and two regional anesthetic techniques, IV regional anesthesia (IVRA) and

axillary brachial plexus block, with respect to clinical outcome, time efficiency, and hospital cost. He found that regional anesthesia is associated with a more favorable patient recovery profile than GA, requiring less nursing care in the PACU and an earlier hospital discharge. These findings were re-demonstrated a few years later by McCartney et al [14] in a prospective randomized trial of 100 ambulatory hand surgery patients showing that single-shot axillary brachial plexus block significantly reduces pain in the immediate post-op period, reducing PACU times, total hospital time and increasing time to first analgesic request before discharge. However, when they tracked patient-reported pain beyond the immediate post-op period they found no difference in pain level on postoperative day 1 or up to 14 days after surgery when compared with GA.

Peripheral Regional Blocks

Single-injection plexus blocks are currently the most commonly used modality for regional anesthesia in upper-extremity surgery. First performed by the American surgeon William Stuart Halsted in 1885, it involves injecting a local anesthetic in the area of the brachial plexus which can provide analgesic effects from 12 to 24 hours [15] [16]. Depending on the surgical area, this can be administered as an intrescalene, supraclvicular or infraclavicular block. The most common block is the interscalene block that affects the root-trunk level of the brachial plexus and can be used for procedures involving the shoulder, proximal aspect of the humerus, and distal aspect of the clavicle but is inadequate for procedures that are distal to the elbow. The supraclavicular block that affects the anterior and posterior divisions of the

trunks of the brachial plexus, as well as the infraclavicular nerve block that targets the brachial plexus at the level of the cords before the exit of the axillary and musculocutaneous nerves is well suited for procedures involving the arm, elbow, forearm, and hand. Finally the suprascapular and axillary nerve blocks have a similar coverage with the interscalene block and can be an effective option for intraoperative and postoperative pain control for shoulder procedures.

Overall peripheral nerve blocks can offer cost effective pain control for patients undergoing upper extremity procedures and have the potential to minimize need for narcotic use, shorten hospital stays and increase patient satisfaction [9]. Nevertheless, a number of complications have been reported with the use of these blocks that include pneumothorax, recurrent laryngeal nerve blockade phrenic blockade, peripheral neuropathy, spinal cord damage and sympathetic chain blockade [17]. With the use of ultrasonographic guidance the safety of peripheral nerve blocks has been enhanced and allowed for the more accurate placement of the blocks with lower anesthetic volumes.

Intravenous Regional Anesthesia (IVRA)

Intravenous Regional Anesthesia (more readily know as the Bier block) was first developed by Dr. August Bier in 1908, and still remains an effective regional anesthesia technique frequently used for upper extremity surgery. It generally involves placement of a tourniquet above the elbow, exsanguination of the extremity with an esmarch and tourniquet inflation to ensure arterial occlusion

followed by slow injection of an anaesthetic agent (typically Lidocaine) into the iv cannula of the surgical hand [18].

This technique is intended to provide a bloodless field with rapid onset, high reliability complete anesthesia, eliminating the need for general anesthesia while leaving local tissue or anatomic structures undistorted [19]. However, this technique is often associated with tourniquet pain and in many cases the patient still requires sedation [20] which is associated with all the well-described side effects of nausea, vomiting and decreased cognitive function. These side effects, along with failure to provide adequate postoperative analgesia [21] ultimately impacts time to discharge. In an effort to improve the quality of the block, over the years various adjuvants have been added to the local anesthetic solution including opioids, non-steroidal anti-inflammatory drugs, [alpha]$_2$-adrenergic agonists, sodium bicarbonate, and muscle relaxants [21] with varying degrees of success.

Another concern associated with the Bier block is its potential to cause both local and systemic pharmacologic toxicity as the tourniquet is deflated and various serious complications and death have been reported in the literature {Reynolds:1984tm}. Guay et al [22] recently performed a systematic review of the adverse events associated with intravenous regional anesthesia (Bier block) and describes cases of local anesthetic toxicity, seizures, compartment syndrome, cardiac arrests and deaths. Interestingly seizures have been reported even with lidocaine at its lowest effective dose (1.5 mg/kg). He concluded that even though serious complications might result from the utilization of the Bier block, their

incidence is relatively low and therefore this technique can be considered a safe method of providing anesthesia during surgery. To minimize these risks, precautionary measures have been described when using this technique. To reduce the bolus effect of the anesthetic agent as it is released into the general circulation [19], cyclical release of the tourniquet is most times necessary. Additionally, a minimum tourniquet time of 30 minutes is required when using a Bier block [23] ensuring enough diffusion of the total anesthetic agent before allowing its systemic distribution. This limitation makes the use of the Bier block impractical for short procedures such as carpal tunnel releases etc further narrowing its indications in outpatient hand procedures.

In recent years there has been a revived interest in the reviving and enhancement of the Bier block. Investigators have described modifications to the Bier technique such as placing the tourniquet distal to the elbow while reducing the amount of lidocaine used to achieve adequate anesthesia. Arslanian et al [23] describe their experience with forearm Bier block in 121 procedures performed and interviewed by telephone 24 hours postoperatively. They report that all patients received adequate anesthesia from the block with no intraoperative or postoperative complications. They were also able to reduce tourniquet time to about 10.1 minutes using this technique.

Another area of adjustment, has been in the choice of anesthetic agent. Meprivacaine, prilocaine, and bupivacaine [24] or use of adjunctive analgesics such as ketorolac and combinations thereof [25] have been described in the literature to

provide varying durations of action and blockade. Opioids including morphine [26] ,fentanyl [27] sufentanil, and meperidine have been added to the IVRA solution with contradictory results [28]. Invariably, regardless of the mixture used one important disadvantage of this technique remains the rapid onset of pain at the operative site after the tourniquet has been deflated {Ceremuga:1998to}. Nonetheless, lidocaine, which is typically given as 0.5% plain lidocaine at a maximum dosage of 3 mg/kg, still remains one of the more common anesthetics used for the Boer block due to its low potential for systemic toxicity.

Wide awake surgery

Wide-awake hand surgery (WAHS) was first introduced by Lalonde in 2007 [29] and it involves the use of local anaesthetic with adrenaline or epinephrine directly into the surgical field. Epinephrine is a potent vasoconstrictor, which decreases the bleeding in the surgical field thus avoiding the need for a tourniquet that is known to cause considerable discomfort. This idea became possible after the emergence of recent evidence suggesting that it is safe to inject epinephrine (adrenaline) in the human finger, once thought to lead to digital ischemia and necrosis [30-32]. Lidocane provides local anesthesia allowing patients to remain comfortable through simple operations such as CTR or Dupytrens as well as more complex surgeries such as arthroplasties [33] and tendon transfers circumventing the need for regional anesthesia, general anesthesia and sedation and hence all the risks associated with these. In fact, Lalonde et al [34] claims that this approach can be used for up to 95% of all hand surgery procedures. In a recent article in the Journal of Hand Surgery [35], he

describes the ideal dosage and location for placement of the injection for various procedures and serves as a good resource and guide for hand surgeons. Further advantages of WAHS, include significant savings in cost and since no anesthesia is administered it eliminates pre-assessment visits, and pre-operative investigations [36-39] . Bypassing pre-operative testing opens up the possibility for patients with significant comorbidities that would otherwise be denied surgery due to the risk of anesthesia, to safely undergo hand procedures. An added benefit is that since patients are awake during the procedures, they can receive education about their surgery and post-operative management but can also participate by actively flexing and extending the digits so the surgeon can evaluate, for example, whether a tendon repair fits through the pulleys intra-operatively.

Elimination of anesthesia also means that patients can practically get up after surgery and go home with no need for extensive PACU care, medication administration and the associated side effects such as drowsiness, nausea or vomiting. In a prospective cohort study by Davison et al [40] that compared 100 consecutive CTRs done with only lidocaine and epinephrine to 100 consecutive CTRs done with IV sedation, they found that 93% of the patients in either group would choose the same method of anesthesia they received again demonstrating that people would choose the method that they are more familiar with. More importantly they found that wide-awake patients spent less time at the hospital than sedated patients (2.6 hrs vs 4.0 hrs) and that only 3% of wide awake patients required preoperative testing (blood work, electrocardiograms, and/or chest radiographs) as compared to 48 % of sedated patients. Additionally, preoperative

anxiety levels for wide-awake patients were lower than for sedated patients even though postoperative anxiety was similar. Narcotics were used by only 5% of unsedated patients as opposed to 67 % of sedated patients despite reported adequate pain control by 89 % and 90 % of patients, respectively. Surprisingly, post-operative nausea and vomiting (PONV) incidence was very low for both groups in this study (1% and 7%) unlike most other previous studies [41] that demonstrate higher incidence of PONV in patients that receive sedational anesthetic causing unplanned admissions and greater dissatisfaction.

POST-OPERATIVE ANALGESIA

PACU

Effective pain management in the PACU can have a big impact on patient satisfaction, time to discharge and their post-operative course once they go home. Morphine and fentanyl are widely used in ambulatory patients to provide analgesia during Phase I recovery. Fentanyl has been advocated due to it's a faster onset time and therefore the more rapid control of pain, potentially avoiding total opioid dose and related side effects. Claxton et al [42] compared the use of intravenous morphine and fentanyl after painful ambulatory procedures in a prospective randomized trial and demonstrated that morphine produced a better quality of analgesia but was associated with an increased incidence of nausea and vomiting, the majority of which occurred after discharge. They concluded that the reduced side effects in combination with a short duration of action of fentanyl may facilitate earlier

discharge and produce fewer complications after discharge.

Home Analgesia

Oral analgesia is the mainstay of pain control once the patient leaves the hospital. Medications prescribed should allow the patient to perform normal activities of daily living, produce minimal side-effects, not interfere with the healing process and be easy to manage by the patient. Depending on the type of procedure performed, breakthrough medications might also be indicated to keep pain under control in case that the prescribed analgesic is ineffective. Postoperative pain after ambulatory hand surgery is typically managed with a combination of oral medications including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioid-containing oral analgesics (e.g., codeine-acetaminophen). Regardless of the choice of medication, patient education on what to expect, ways to manage pain and how to use the medications prescribed, remains paramount.

Acetamenophen

Acetamenophen (or paracetamol) is one of the most widely used analgesics worldwide. It is effective, safe, cheap with a favorable adverse effect profile [43]. Yet, its mechanism of action is poorly understood. There is some evidence that it has a central antinociceptive effect and some of the proposed mechanism of action include inhibition of COX-2 in CNS or inhibition of putative central cyclooxygenase ''COX-3'' [44], [45]. There is also some evidence that it modulates inhibitory serotonergic pathways and may also prevent prostaglandin production at the cellular level. It is

known that unlike NSAIDs, it does not irritate gastric mucosa, affect platelet function or cause renal insufficiency making it a very versatile medication.

NSAIDs

Prostaglandins, and their role in pain modulation, were first discovered in the 1960s. Shortly after, in 1965, Sir John Vane first demonstrated the *in vivo* reduction in prostaglandin levels by inhibition of prostaglandin synthetase, now known as cyclooxygenase (COX) [46]. Once this enzyme was identified, the nonsteroidal anti-inflammatory drugs (NSAIDs), were developed to inhibit it. Even though some central action has been reported [47], the generally accepted mechanism of action of NSAIDs today, remains the attenuation of prostaglandin synthesis by inhibition of cyclooxygenase (COX) enzymes [48].

NSAIDs are now part of most day surgery pain regimens. Their anti-inflammatory properties not only provide pain relief but may help reduce local edema and minimize the use of more potent drugs. The 1998 guidelines for the use of NSAIDs in the perioperative period, issued by the Royal College of Anaesthetists, stated that based on the strongest evidence available, ‘‘in situations where there are no contraindications NSAIDs are the drug of choice after many day-case procedures’’ [7]. Today is estimated that 20-30% of Americans use an NSAID each year, and 1-2% use NSAIDs every day [49].

Despite their success, one of the main concerns with the use of NSAID remains their gastrointestinal toxicity, which led to the exploration of ways to reduce their side-

effect profile. The two COX isoenzymes were discovered in the late 1980s, with COX-1 largely involved in homeostasis, including the maintenance of gastroprotective mechanisms and renal blood flow; and COX-2, which is upregulated during the inflammatory response. COX-2-selective drugs emerged shortly after which the World Health Organization has categorized as a new subclass of NSAIDs (coxibs). Despite continuing controversy over the safety of the coxibs and concerns of a higher risk of myocardial infarction there appears to be no clear differences in the cardiovascular risks of the currently available coxibs and the non-selective NSAIDs when used at the recommended doses [46]. On the other hand, even with a favorable side-effect profile, they perform equally as well as the ns-NSAIDs. In a recent systematic review by Romsing et al [50], they showed that Rofecoxib 50 mg and parecoxib 40 mg have an equipotent analgesic efficacy relative to traditional NSAIDs in post-operative pain after minor and major surgical procedures.

Ketorolac

Ketorolac is a newer nonsteroidal anti-inflammatory drug (NSAID) analgesic, considered a central nervous system agent [51], that was first approved for use by the U.S. Food and Drug Administration in 1997. Similar to classic NSAID's, when co-administered with an opioid, it exhibits marked opioid-sparing effects, allowing a 25% to 50% reduction in opioid requirement [51]. A randomized double-blinded study by Kinsella et al [52], demonstrated that morphine requirements were 3 times

less in the first 24hrs in patients having major orthopedic procedures who had adjuvant ketorolac administered during the postoperative period.

Since it acts by inhibiting the cyclooxygenase pathway it is therefore also a potent inhibitor of platelet aggregation and some concerns were raised with its use in the perioperative period. Even though there is a paucity of literature in the use of ketorolac with hand procedures in particular, it has been looked at in the spine literature where Chin et al. [53] found no risk of bleeding complications compared with that of their control group in patients having microdiscectomy after a single intraoperative dose of ketorolac.

For all NSAIDs, careful patient selection is important. Specifically, a history of coronary artery disease, gastrointestinal risk factors such as gastric ulcers and renal insufficiency has to be taken into consideration before prescribing ns-NSAIDs, C OX-2 selective inhibitors or ketorolac. After weighing the risks and benefits, NSAID's, when used at the right dosing, remain one of the most effective analgesics and anti-inflammatory medications that can safely be used for post-operative analgesia after hand procedures.

Opioids

Even though opioids are commonly used in ambulatory surgery procedures in the USA, their role is sometimes questioned because of their well known side effects of nausea, vomiting, sedation, dizziness, respiratory depression and substance

dependence [54]. Weak opioids such as codeine and tramadol are commonly used and are often times prescribed in combination with acetaminophen. In a controlled trial [55], postoperative pain management at home using either tramadol, metamizol, or paracetamol as single substances after ambulatory hand surgery has been shown to be inadequate for up to 40% of all patients. Consequently, there has been an increasing focus on combining analgesic medications with different mechanisms of actions and complementary pharmacokinetic profiles in hopes to not only achieve greater efficacy but also a better safety profile [56]. For example in a randomized, double-blind, multicenter trial comparing the efficacy and safety of tramadol HCL 37.5 mg/paracetamol 325 mg combination tablet with tramadol HCL 50 mg capsule in the treatment of postoperative pain following ambulatory hand surgery it was found that analgesic efficacy of the two treatments was comparable but multiple-dose tramadol/paracetamol treatment showed a better safety profile than tramadol monotherapy [57].

FUTURE DIRECTIONS

Extended, complete and safe pain relief without the need for oral medication and minimal effort from the patient are the desired characteristics of an ideal analgesic strategy/ system. Oral or intravenous analgesics are by definition systemic medications and invariably associated with side-effects. One also has to consider possible medication interactions, use of concurrent anticoagulation and any pre-existing conditions or comorbidities as these can affect the clearance and effective dosing of the analgesic used. A local or peripheral analgesic strategy circumvents

(or at least minimizes) the need for systemic medications and can potentially not only prevent the associated side-effects as well as potential medication interactions but also relies less on patient compliance and requires less customization from patient to patient.

Continuous Peripheral Nerve Blockade (CPNB)

This strategy for post-operative analgesia entails the percutaneous insertion of perineural catheters close to the peripheral nerve of interest and the continues infusion of local anesthetic to achieve blockade in its corresponding distribution. Richman et al [54], conducted a meta-analysis of randomized controlled studies comparing the effectiveness of CPNB and opioids. He identified 19 studies (12 of which for upper extremity procedures) including more than 600 patients and revealed that CPNB provided better postoperative analgesia compared with opioids at 24 h, 48 h and 72 hrs post-operatively. Furthermore, significant reduction in opioid use (when used as a rescue medication) was noted in patients receiving perineural analgesia with fewer opioid-related side effects.

However, variable success rates of CNPB have been reported in the literature. In a single-center, prospective, double-blind, randomized and placebo-controlled study, Goebel et al [58] comparing single-shot and CPNB by insertion of an patient-controlled interscalene catheter that contained either 0.2% ropivacaine (catheter group) or normal saline solution (single-shot group) after major open-shoulder surgeries. They showed that there was significantly less consumption of rescue medication in the catheter group, but only within the first 24 h after surgery; opioid use past day 1

was equal in the 2 groups and incidence of side effects did not differ between the two groups.

Catheter patency or secondary catheter block has been identified in many studies as a major mode of failure of CPNB with rates ranging from 10%-20% [59-61]. Event though most studies have been limited by small patient samples one of the largest studies published comes from the hand literature by Ahsan et al [62] that retrospectively explored the incidence of failure in 207 patients that received infraclavicular or supraclavicular CPNB for postoperative analgesia after upper extremity procedures. In their series, CPNB failure rate for infraclavicular and supraclavicular catheters was 19% and 26%, respectively. Other mechanisms of CNPB failure that have been reported and could explain these results include catheter migration [63], fluid leakage at the catheter site [59] and dislodgement or obstruction of the tubing [64]. Incorrect catheter placement [65], despite the significant increase in placement accuracy with the use of ultrasound guidance, also still remains an issue.

In addition to the failures associated with the pump, catheter and block placement, CPNB use is not innocuous. Serious complications have been reported such as peri-catheter hematoma formation and intravascular puncture [66], myonecrosis, systemic or local anesthetic toxicity and prolonged Horner syndrome [67]. The presence of a catheter that violates the skin also raises the concern for introduction of bacteria to the area, and infection rates after catheter placement has been reported to be 0%-3% [68].

Furthermore, their satisfactory function relies on the patient to take care of the pump at home. In order to implement these systems in the ambulatory setting, one must assure that the patient's are very well educated on how to care for them and make sure there is a very stringent follow up system in place.

DepoFoam (Exparil)

Multiple attempts have been made to extend the effect of local anesthetics and blocks to attain longer local regional anesthesia in the early post operative period decreasing the need for oral systemic narcotics and non-opioid analgesics, such as NSAIDs. Despite multiple efforts and approaches with the use of adjuvants, vehicles and gel formulations of classic analgesics and anesthetics the typical duration of adequate pain control has been a maximum of 24 hrs.

DepoFoam® bupivacaine (Pacira Pharmaceuticals, Inc., San Diego, CA, USA) or more widely known as Exparel, is a novel extended-release liposomal bupivacaine-based analgesic. It was granted FDA approval in 2011 and is indicated for postsurgical analgesia, designed for single-dose local administration into the surgical wound [69]. The extended-release formulation consists of microscopic, spherical, lipid-based which allows for diffusion of bupivacaine over an extended period, resulting in pain relief for up to 96 hours after surgery. This is in contrast to infiltration with classic local anesthetic agents (eg, bupivacaine HCl, ropivacaine) that are widely used today resulting in analgesia that is generally limited to about 8 hours or less.

In a recent randomized, multicenter, double-blind phase 3 clinical study [70], Exparel

was compared with placebo for the prevention of pain after bunionectomy. Using a numeric rating scale (NRS) for pain, scores were significantly less in patients treated with DepoFoam bupivacaine as compared to patients receiving placebo at 24 hours and 36 hours. They also found that more patients in the Exparel group avoided use of opioid rescue medication during the first 24 hours and were pain-free up to 48 hours after surgery. Moreover, fewer adverse events were reported by patients treated with DepoFoam bupivacaine (59.8%), versus placebo (67.7%). Portillo et al [71] just completed their systematic review of prospective studies on the use of DepoFoam and the analysis of the incidence reported adverse effects when compared to conventional bupivacaine or placebo. They looked at DepoFoam use in knee arthroplasty, hemmorrhidectomy, augmentation mammoplasty, bunionectomy and healthy volunteers. They found that DepoFoam bupivacaine used in therapeutic doses was well-tolerated, and showed a favorable safety profile compared to bupivacaine and controls.

To the best of our knowledge, no studies have been conducted to date that explore the use of exparil specifically in hand surgery. Such studies are needed to validate the use of this promising technology in our patients.

Extended Peripheral Nerve Blocks

Currently available local anesthetics approved for single-injection peripheral nerve blocks have a maximum duration of <24 hours. Just as in the case of extended local anesthesia, attempts have been made to prolong the duration of peripheral nerve

blocks with the use of various vehicles such surgically implantable pellets [72], hyaluronic acid matrices [73] or lipid-protein-sugar particles [74] just to name a few. However, clinical translation and wide adoption of such systems of sustained release formulations for local anesthetics has mostly been limited by adverse tissue reaction with reports of myotoxicity, inflammation, and neurotoxicity.

Exparil, which is known to release for at least 96 hours after injection, is currently FDA-approved exclusively for wound infiltration but not peripheral nerve blocks [75]. Some information of the use of Exparel in nerve block fashion however, has started to emerge in recent years. In the field of plastic surgery, Morales et al [76] reports their experience with 64 female patients who received liposomal bupivicaine injections in an abdominal field block fashion for abdominoplasty with rectus plication. Based on their postoperative data and questionnaires, these patients experienced reduced postoperative pain, required less postoperative narcotic medication, and resumed both earlier ambulation and normal activity. Furthermore, Ilfeld et al [75] administered bilateral single-injection liposomal bupivacaine femoral nerve blocks in 14 healthy volunteers. Using the maximum voluntary isometric contraction of the quadriceps femoris muscle and tolerance to cutaneous electrical current in the femoral nerve distribution as end points, they report partial sensory and motor block of >24 hours.

Exparil's biocompatibility near nerve tissue is not well characterized but a few studies have began to look at the safety in such scenarios. McAlvin et al [77] injected

Exparel close to the sciatic nerves in rats and compared its effects to that of different concentrations of bupivacaine HCl. They found that even though Exparel injection caused a longer sciatic nerve blockade, median inflammation scores determined by histologic sections four days after injection, were slightly higher. However, myotoxicity in all groups was not statistically significantly different and no neurotoxicity was detected in any group.

Richard et al [78], performed single-dose toxicology studies of 3 doses of Exparil (9, 18, and 30mg/kg), and compared them to bupivacaine solution (9 mg/kg) and saline. When these were injected around the brachial plexus nerve bundle of rabbits and dogs, they found that at the same dose, Exparel resulted in a 4-fold lower maximum plasma concentration of bupivacaine and was well tolerated at all doses. Histopathology evaluation on Day 3 and 15, only revealed minimal to mild granulomatous inflammation of adipose tissue around nerve roots and concluded that it did not produce any nerve damage in their model.

Exparel continues to be actively investigated for postsurgical analgesia via peripheral nerve block [78] and so far 2 phase 1 studies have been completed and, based on the safety data, the FDA has now approved subsequent phase 2 and 3 trials. If this, along with other newer analgesics continue to prove safe and efficacious, we may soon be able to provide long lasting pain relief to patients undergoing ambulatory hand procedures, without the use of oral medications and hence without their well described side-effects.

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