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ANDROLOGY

Original Article

Long-acting liposomal bupivacaine decreases inpatient narcotic requirements in men undergoing penile prosthesis implantation

Uzun etkili lipozomal bupivakain penil protez implantasyonu yapılan hastaların hastanedeki narkotik analjezik gereksinmelerini azaltmaktadır

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ABSTRACT

Objective: A new extended-release bupivacaine suspension bupivacaine (ERSB) delivers 3 days of local anesthetic and has been shown to reduce pain and narcotic usage in some patient groups but this issue is largely unstudied in urologic surgery.

Material and methods: We performed a single-surgeon retrospective chart review of the patients who underwent penile prosthesis implantation. Pain scores and standardized morphine equivalent (ME) dose data were collected during 23 hour-observation period. Subjects who received ERSB were compared with those who received standard bupivacaine or no local anesthesia.

Results: In a study population of 37 patients, those who received (n=13), and did not receive (n=24) ERSB were grouped, respectively. The groups were comparable demographically. ME was used 3.2 fold more frequently in the non-ERSB group (18.0, and 5.6 for non-ERSB, and ESRB groups, respectively (p=0.04). Mean overall pain scores were 3.8/10 for ERSB and 3.9/10 for non-ERSB group, respectively. Per patient medication cost for the control, and ERSB groups were $5.16 and $285.54, respectively.

Conclusion: The use of a new ERSB in penile prosthesis implants did lead to reduced narcotic consumption with comparable postoperative pain control to the non-ERSB group. However, the cost of the ERSB ($285/dose) may be prohibitive for its use.

Keywords: Erectile dysfunction; liposomal bupivacaine; local anesthetic; penile prosthesis.

ÖZ

Amaç: Yeni bir uzamış salımlı bupivakain süspansiyonu (USBS) 3 günlük lokal anestezik etki sağlamakta olup; bazı hasta gruplarında ağrı ve narkotik analjezik kullanımını azalttığı gösterilmiş olmasına rağmen ürolojik cerrahide geniş ölçüde çalışılmamıştır.

Gereç ve yöntemler: Penis protezi implantasyonu ameliyatı geçirmiş hastaların hastane kayıtları geriye dönük olarak gözden geçirilmiştir. Hastaların 23 saatlik gözlem dönemleri boyunca ağrı skorları ve standardize edilmiş morfin eşdeğer dozlarına ilişkin veriler toplanmıştır. USBS uygulanan hastalar herhangi bir lokal anestezik kullanılmayanlar veya standart bupivakain kullanılanlarla karşılaştırılmıştır.

Bulgular: Toplam 37 hastadan USBS kullanılan 13 ve kullanılmayan 24 hasta birbirleriyle karşılaştırılmıştır. Gruplar demografik açıdan benzerdi. Ortalama morfin eşdeğeri analjezik kullanımı USBS uygulanmayan grupta 3,2 kat daha yüksek orandaydı (USBS uygulanmayanlarda 18,0'e karşın USBS uygulananlarda 5,6 (p=0,04). USBS uygulanan ve uygulanmayan gruplarda ortalama genel ağrı skorları sırasıyla 3,8/10 ve 3,9/10 şeklindeydi. (istatistiksel açıdan anlamlı değil). Kontrol ve USBS gruplarında hasta başına ilaç maliyetleri sırasıyla 5.16 $ ve 285.54 $ idi.

Sonuç: Penil protez implantasyonunda yeni USBS kullanılması, USBS kullanılmayanlara göre postoperatif ağrı kontrolü için narkotik analjezik tüketimini gerçekten azaltmıştır. Ancak USBS'nin yüksek maliyeti (tek dozu 285$) kullanımını kısıtlayabilir.

Anahtar sözcükler: Erektil disfonksiyon; lipozomal bupivakain; lokal anestezik; penil protez.

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Introduction

For men with erectile dysfunction refractory to first and second line treatment modalities the inflatable penile prosthesis (IPP) has become the definitive treatment. Patient and partner satisfaction rates are remarkable for the IPP, trumping oral medications, intracavernous injections, and vacuum erection devices.[1] The success of the penile prosthesis hinges on its reliable mechanical function and low rates of infection.[2] However, in our practice, preoperative anxiety and post-implantation pain remain a considerable factor in patient satisfaction and acceptance of the device.[3]

Postoperative pain after IPP implantation is common but variable in duration. Most of our patients report 1-2 weeks of pain requiring oral narcotics. Within 6 weeks of implantation, most of them will no longer require narcotic- based pain medications and will resume their normal activities. The penoscrotal approach usually produces pain in the scrotum under the incision and the implant pump. Locally acting injectable anesthetics have been shown to minimize this discomfort[4], but there is a surprising lack of randomized trials assessing these medications. A new extended- release suspension bupivacaine (ERSB) has recently become available. This medication is contained within liposomes and allows for a prolonged time release leading to approximately three days of local anesthetic effect.

While ERSB has been studied in patients for postoperative pain[5], there are currently no studies assessing ERSB in controlling postoperative pain in patients undergoing implantation of IPP. These medications could have a potentially impressive role in controlling pain as this procedure has been previously done exclusively under local anesthesia.[6] Narcotic- based oral pain medications are not without risk and maximizing perioperative pain control with this new medication could minimize this risk. However, this novel local anesthetic formulation is costly and its utility will be ultimately determined by the significance of pain control relative to its cost-effectiveness.

We set out to review the utility of this new medication by examining the immediate postoperative course of patients who underwent IPP implantation at our institution with a comparison to a control group of men who underwent implantation during the same time period.

Material and methods

Data collection

After receiving approval from our institutional review board, we retrospectively reviewed charts of a single surgeon (TSK). Patients' data were collected from electronic medical records and billing sheets at the operating surgeon's clinic and hospital. Patients were identified by CPT code from our billing department. The senior author offered all standard treatments for erectile dysfunction to patients (i.e. oral medications, intracavernosal injections, etc). Generally, patients in our practice who pursue IPP have failed multiple other treatments.

Study population

We identified patients who underwent penoscrotal implantation of a 3-piece IPP at our institution within a 6 month period. Patients who had undergone IPP revision surgery were excluded from our study, as a revision operation is associated with increased tissue manipulation and subsequent pain. Also excluded were patients on a home dose of narcotics due to the confounding effects of opiate tolerance.

Surgical technique

All patients received general anesthesia for the procedure. Additionally, 20 cc of ERSB (medication mixed with normal saline to produce a total volume of 20 cc) were utilized for periincisional block prior to incision, and bilateral cord blocks. The anesthetic mixture was administered into the corpora, in the reservoir space, and a generous portion in the area of anticipated pump location. The control group received standard bupivacaine or did not receive any anasthetic. In all patients ERSB was administered using EXPAREL® DepoFoam® delivery system (Pacira Pharmaceuticals, Inc., San Diego, CA, USA).

Outcome measures

During the postoperative observation period data on pain scores and narcotic pain medication were collected. Pain scores were recorded from nursing assessments and the standard scale from 0 to 10 was utilized. We customarily observe our patients 23 hours after IPP implantation. Patients are seen the following morning after surgery for compressive "mummy wrap" dressing exchange, and bladder catheter and drain removal.

Data about hospital medication cost were collected in both groups including i.v. and oral pain medications. Due to variability in the potency of narcotic- based pain medications, we converted all narcotic pain medications to a standard morphine equivalent (MEq) dosing for comparison and statistical analysis. Information on postoperative oral narcotic refills was also obtained. Decision to administer in- hospital narcotics was at the discretion of the caretaker nurse who utilized nursing protocols and patient self-reported pain scores.

Statistical analysis

Groups were compared using Student's t-test. Statistical analysis was completed using GraphPad Prism version 6 (GraphPad Inc., California, USA).

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Results

A total of 40 patients were identified. Two of these were revisions and one patient had significant previous narcotic use leaving 37 patients in the study group. Of these 37 patients, 13 men received ERSB and 24 men did not receive ERSB for placement of IPP. Groups were comparable with no statistical difference in age, body mass index (BMI), smoking status or medical comorbidities (Table 1).

Mean overall pain scores were 3.8/10 ERSB and 3.9/10 non-ERSB during the postoperative course (p= NS, Table 2). Subjects in the non-ERSB group required 3.2 times more morphine equivalents than the ERSB group with 18.0 vs 5.6 ME doses utilized, respectively (p=0.04, Table 2). There were no statistically significant differences in the number of outpatient narcotic refills obtained between groups.

The per patient medication cost for the control group was $5.16 and $285.54 for the ERSB group. In the ERSB group, ERSB medication cost was responsible for the greater part of the hospital expenditures ($285 per dose).

Discussion

Use of various multimodal analgesic models often utilizing perioperative local anesthetic has been attempted in an effort to improve overall pain control. The primary determinative factor on the duration of local anesthetic effect is the drug's rate of diffusion and absorption. Local anesthetics vary in duration of action, including short-acting lidocaine (1-2 hrs), intermediate-acting mepivacaine (2-5 hrs) and long-acting bupivacaine (8-12 hrs).[7]

In recent years, new formulations of long-acting anesthetics have become available including ERSB which is formulated to be contained in liposomes (consisting of a lipid bilayer surrounding an aqueous core).[8] The multivesicular liposomes allow an extended release of medications, as the drug is released initially from the external vesicles and then redistributed into the internal vesicles until all the drug is released over time (roughly 96 hours).[9,10] The ERSB formulation used in this study has previously been approved by the FDA for use for the relief of postoperative pain after bunionectomy and hemmorhoidectomy after it was shown to significantly reduce pain scores, time to first opioid use, and overall opioid consumption.[11,12] As ERSB is simply a different formulation of conventional bupivicaine, toxicities are consistent with those previously described for bupivicaine. In clinical trials, the most common adverse reactions have included nausea, emesis, constipation, headache and dizziness.[13,14] The only injection site effects of ERSB noted in animal studies include a local granulomatous inflammation.[15]

Table 1. Demographic information of groups

	Non-ERSB	ERSB	p
BMI kg/m^2	32.6±6.6	34.1±5.9	0.48
Age (years)	63.5±8.7	64.4±6.1	0.72
Number of comorbidities	3.3±2.0	2.9±1.7	0.62
Active smokers (%)	30	14	0.52
Diabetes mellitus (%)	41	31	0.72
Hypertension (%)	58	50	0.73
Depression/anxiety (%)	17	7	0.63
Hypogonadism (%)	25	21	1.0
Hyperlipidemia (%)	29	21	0.72
CAD (%)	21	21	1.0
Peyronie's disease (%)	17	14	1.0

BMI: body mass index; ERSB: extended- release bupivacaine suspension; CAD: coronary artery disease

Table 2. Overall mean morphine equivalents and pain scores

	ME±SD	Pain score±SD
Non-ERSB	18.0±22	3.9±2.3
ERSB	5.56±6.9	3.8±2.9

ME: morphine equivalents; SD: standard deviation; ERSB: extended- release bupivacaine suspension

Our study found an overall decrease in narcotic consumption in the ERSB group compared with the non-ERSB group during the patients' 23 hour hospital stay. However, a difference in pain scores was not found. Of note is the overall low pain scores under 4 on a scale from 0-10 points reported by both groups of patients. In addition, some of the first data on the cost of ERSB were reported by us. The ERSB group spent an average of $285.54 on total in-hospital pain medication costs, compared with just $5.16 in the non-ERSB group. In the ERSB group, an additional narcotic consumption amounting to a mere $0.54 was spent by our patients compared with $5.16 in the non-ERSB group. This figure includes some patients in the ERSB group who did not require any additional opioid-based pain control postoperatively. While the difference in dollars spent in opioid analgesia between the groups seems minimal, the significance of collateral events such as

adverse drug reactions in either group were not evaluated. Future studies could attempt to capture these potentially important data.

Recent studies performed in patients who had undergone abdominoplasties, open colectomies, and ileostomy reversal procedures demonstrated success with ERSB in reducing postoperative pain.[14-16] In Vogel's study of ERSB use in controlling postoperative pain in ileostomy reversal procedures, significant reductions in postoperative narcotic consumption were reported in the ERSB group opposed to an opioid patient-controlled analgesia (PCA) group.[16] In addition, a reduction of a cost related to length of stay and total hospital costs was found in the ERSB group, although this difference was statistically insignificant. The average length of stay for patients undergoing ileostomy reversal ranges from 4-10 days.[16] In comparison, all of our IPP implantation patients were discharged on postoperative day 1, regardless of the method of analgesia. In addition, many of the previous studies of ERSB including a hemorrhoidectomy trial followed patients through at least 72 hours of hospitalization, which encompasses the full timeframe of ERSB's potential analgesia.[9] Since in our study we observed our patients who had undergone IPP implantation during perioperative period of 23 hours, our study might not capture the entirety of the potential benefits of a longer-acting analgesic. However, we noted no statistically relevant change in the number of outpatient refills requested. This is not surprising since the pharmacological effects of our initially prescribed narcotic dosage lasts well beyond the expected duration of the ERSB.

The vast majority of cost associated with pain control stemmed from the cost of ERSB itself due to the low in-hospital costs associated with other pain medications. Other studies showing a decrease in the hospital cost in the ERSB group also reported a decrease in hospital length of stay, which likely represented the bulk of cost savings.[15,16] Because all of our study participants were discharged on postoperative day 1, in both the study and control group, our cost data were based solely on medication costs. Due to the inherent outpatient nature of the procedure, we were unable to capture additional data about convalescence or missed productivity.

This study represents a likely significant variation in the appropriate utilization for extended-release local anesthetics. Intraoperative anesthesia with a longer acting anesthetic may better serve patients undergoing more lengthy procedures, those with more significant tissue trauma, and a longer postoperative recovery. However, considering the cost of a 23 hour in-hospital observation stay, discharging IPP patients on the same day with acceptable pain control achieved using ERSB may offset the cost of the medication.

Limitations of this pilot study include limited statistical power due to a low number of enrollees and the subjective nature of pain scores. The retrospective nature of the study and a lack of ensured blinding by the urology residents caring for the patients decreased the strength of the conclusions and restricted objective findings reported by the residents. Although the patients' nurses were not intentionally blinded to the identities of the patients who did or did not receive ERSB, it is very unlikely that they would have altered care based on differences in perioperative local anesthetic use. Future studies should seek to increase the sample size of patients, assess pain scores in a more uniform fashion and blind both nurses and residents taking care of the patient to the study protocol.

In conclusion, the use of a new ERSB in IPP led to a 3.2 fold decrease in consumption of narcotics by patients and resulted in equivalent postoperative pain control when compared with traditional postoperative pain control protocols. Considering the cost of the ERSB ($285 per dose) in comparison to the inexpensive i.v. and oral pain medication used, this new medication may not be cost-effective for patients undergoing implantation of an IPP.

Ethics Committee Approval: Due to the retrospective nature of this study, an informed consent exemption was granted in writing from Southern Illinois University School of Medicine IRB. No ethics committee consultation was required.

Peer-review: Externally peer-reviewed.

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