Title: Comparison of 1% Chloroprocaine HCL vs. Bupivacaine Spinal in Patients Undergoing Anorectal Surgery in an Ambulatory Surgery Center: A Double-Blind Randomized Controlled Pilot Trial

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Comparison of 1% Chloroprocaine HCL vs. Hyperbaric Bupivacaine Spinal in Patients Undergoing Anorectal Surgery in an Ambulatory Surgery Center: A Double-Blind Randomized Controlled Pilot Trial.

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Introduction:

Ambulatory surgical procedures continue to rise as hospital, and medical centers are finding ways to improve patients' satisfaction and cut the cost of hospital visit by decreasing inpatient admissions. According to recent reports, between 50% and 70% of all surgeries in North America are currently performed as outpatient procedures.[1] The ideal anesthetic for ambulatory surgery cases includes one that will allow for balanced anesthesia and analgesia, decrease the risk of nausea and vomiting, promote good postoperative pain control, and hasten discharge time. Spinal anesthesia is an excellent option for ambulatory surgery involving cases below the waist such as colorectal surgery (hemorrhoidectomy), gynecological procedures (hysteroscopy, D&C) and orthopedic procedures (knee arthroscopy, ACL, MCL, repairs, ankle surgery). However, some of the characteristics of spinal anesthesia such as delayed ambulation, pain after block regression and risk of urinary retention may limit its use thus the choice of local anesthetic is critical to the success of spinal anesthesia in improving overall patient satisfaction and time of discharge from the outpatient setting.

In the past, long-acting local anesthetics such as hyperbaric bupivacaine, tetracaine, and levobupivacaine were injected intrathecally which resulted in delays in hospital discharge, prolong motor and sensory blockade and an increase in urinary retention. This resulted in studies showing no difference in overall ambulatory surgery unit time between neuraxial technique and general anesthesia.[2] However, in recent years short-acting local anesthetics such as 1% chloroprocaine-MPF (CP), prilocaine, and articaine are used for ambulatory spinal anesthesia because of their fast onset, satisfying block, quick recovery, and minimal side effects.[3] Lidocaine was the choice for short-acting local anesthetic in the past for outpatient procedures; however, due to the significant risk of transient neurological symptoms (TNS), most anesthesiologists have abandoned its use.[4] Now, 1% chloroprocaine-MPF have become perhaps the ideal drug for a short surgical procedure due to the rapid offset of the block.

1% Chloroprocaine is an amino-ester CP local anesthetic with a very short half-life.[5] In early production, sodium bisulfite was added as a preservative, which was set to be the cause of several cases of transient neurologic symptoms in patients that had intrathecal dosing. In recent productions, all preservatives and antioxidants have been removed from two of the three currently available preparations of CP. Preservative-free 1% chloroprocaine has been used in several retrospective and prospective studies, and there has been no evidence of an increase in neurotoxicity or TNS.[6-8] A chart review at the Virginia Mason Medical Center, published in 2004, evaluated the first 122 patients receiving spinal anesthesia with 2-CP, another preservative free chloroprocaine, the authors did not find any transient neurological symptom nor any sign of neurotoxicity.[9] However, postoperative pain and urinary retention have been

shown to exist in patients that undergo spinal anesthesia for surgeries. Most of the patients that had urinary retention underwent surgeries which in itself increase the risk of urinary retention such as transurethral resection of bladder tumor, perirectal surgery, cystoscopy, and hernia surgery. [9-11] It has also been reported that if no surgery-related or underlying risk factors for urinary retention are present and short-acting local anesthetics are used for spinal anesthesia the incidence of urinary retention is acceptably low.[12]

A majority of the studies published in the last ten years are on the use of 2-chloroprocaine in patients undergoing orthopedic, general and gynecological surgery. There is a scarce study on the use of preservative-free 1% Chloroprocaine on colorectal surgery such as hemorrhoidectomies. Although, several studies in Europe have shown its efficacy and safety in spinal anesthesia for lower extremity procedures. In the United States, The Food and Drug Administration (FDA) just approved 1% Chloroprocaine HCL for use in spinal anesthesia and thus we expect to see more clinical publications on its utilization for surgical procedures. As previously mentioned, an ideal anesthetic for spinal anesthesia in ambulatory surgery patients would provide a rapid onset of action, adequate potency, predictable duration, and decreased neurotoxicity and systemic side effects. Thus, we would like to propose a study were preservative-free 1% chloroprocaine HCL will be compared to hyperbaric bupivacaine in ambulatory anorectal surgery. The Primary outcomes will be recovery time (return of motor and sensory function) and fit to discharge time from the PACU. Secondary outcomes will be evidence of hypotension during the case, and evidence of TNS (transient neurologic symptoms) 24hr after the procedure.

Hypothesis

The use of 1% Chloroprocaine HCl spinal anesthesia will reduce the recovery times and discharge time of patients undergoing hemorrhoidectomies as compared to 0.75% bupivacaine spinal.

Primary Objective

The primary objective is to compare the recovery times (return of motor and sensory function), time of ambulation, and discharge time between 1% Chloroprocaine and 0.75% bupivacaine spinal anesthesia for anorectal surgery.

Secondary endpoints:

To evaluate the incidence of intraoperative hypotension after the use of 1% Chloroprocaine vs. 0.75% bupivacaine spinal.

To evaluate the incidence of transient neurologic symptoms 24hrs postoperative.

Design and Methods

This is a randomized, prospective study assigning patients to either 1% Chloroprocaine HCl or 0.75% bupivacaine spinal anesthesia group. Consents for participation in the study will be obtained during the patients' preoperative anesthesia evaluation. There will be no change in the primary anesthetic technique (spinal anesthesia) since these patients routinely get spinal anesthesia for a variety of

anorectal procedure. However, there would be a change in the type of local anesthetic administration. On the day of surgery, consented patients will be randomized to one of the two groups. The patients, the researcher who recruited the patients and collected the data, will be blinded. Also, the Nurse Anesthetists in the operating room taking care of the patient, the discharge Anesthesiologist, and the PACU nurse will all be blinded. The only unblinded individual will be the operating room Anesthesiologist (a different physician from discharge anesthesiologist) performing the spinal. **(Research assistant will hand an enclosed envelope to the anesthesiologists performing the spinal anesthesia with the name of local anesthetic to use).**

Postoperatively, the PACU nurse will be asked to document the return of motor and sensory function, time of ambulation, in addition to voiding time. At the time of voiding, the nurse will be asked to inform the discharging anesthesiologist (not involved in the case) for a postoperative evaluation and a discharge note. Although the ability to void is not a required discharge criteria from an ambulatory surgery center, if a patient cannot void once they are able to ambulate, a bladder scan will be performed, surgeon notified if bladder distention (>300 ml), catheterization per surgeon order, and the patient will be sent home and informed if he or she cannot void spontaneously after 8 hours of catheterization, they then should notify the surgeon and go directly to the emergency department. If a Foley catheter was placed, the patient will then follow up with the surgeon the next day in the office.

For postoperative data collection, the routine 24hr postoperative phone calls in which nurses make to patients will be utilized. However two additional questions will be asked, 1-the presence of nerve pain in the buttocks and thighs shooting down their legs unilaterally or bilaterally, 2- Inability to void, pass flatus or defecate. If any of the symptoms are present, then the nurse will inform an anesthesiologist (**not involved in the case**) who will give the patient a call and advise them on the treatment protocol. The research assistant will then be informed by the anesthesiologist who made the phone call.

Inclusion criteria

Patient undergoing Anorectal Procedures

Age 18 and above

ASA, I-III

Exclusion criteria

Patient refusal

Inability to understand and sign informed consent

Allergic reaction to bupivacaine or other local anesthetics

Coagulopathy (INR greater than or equal to 1.5)

Use of anticoagulant drugs (Plavix, Coumadin)

Thrombocytopenia (Platelets < 100,000)

Infection at the site

Increased intracranial pressure

Unstable spine, Spine abnormalities

History of atypical cholinesterase (CP is metabolized by cholinesterase)

Diagnosis of any disorders (i.e., benign prostatic hyperplasia, cystitis, vulvovaginitis) that would delay voiding

Anticipated procedure time longer than 60 minutes

Intraoperative management

All patients will receive mild sedation for spinal anesthesia (2mg midazolam and propofol infusion). All patients will get spinal anesthesia. One group of patients will get 5ml (50mg) of 1% Chloroprocaine HCl, and the other group will get 0.8ml of 0.75% hyperbaric bupivacaine. No narcotics or epinephrine will be added to the spinal. Patients will be monitored intraoperatively with standard ASA monitors and data collection will be done with the epic electronic record. Any hemodynamic instability will be treated accordingly. The operating room anesthesiologist performing the neuraxial anesthesia will be aware of the local anesthetic administered intraoperatively. However, the research assistant, patient, PACU nurse, and discharge anesthesiologists will be unaware of which local anesthetic was administered.

Post-operative pain management

All patients will be written for standard postoperative adult anesthesia order. This will include antiemetic, fluid and pain medication. Each patient will receive one dose of a non-steroidal anti-inflammatory drug (NSAIDs), i.e. ketorolac and as needed dose of 25mcg of fentanyl q5mins max dose 5.

Outcomes measure assessments

A research assistant, who is blinded to the group, will record the return of sensory, motor, ambulation, voiding and discharge times. The incidence of hypotension will be documented if systolic blood pressure after spinal drops to more than 20mmhg from baseline (Systolic blood pressure three minutes prior to spinal block). On post-op day 2, the research assistant will contact the patients and ask a series of standard questions (see below) to determine if postoperative transient neurological symptoms (TNS) occurred. Transient neurologic symptoms will be defined as back pain or dysesthesia that radiated to the buttocks, thighs, hips, or calves and began within the first 24 h after surgery. Localized pain or tenderness at the injection site or lower back without radiation will not be considered TNS. If postoperative TNS exist, but the pain is mild, no treatment is required only reassurance to the patient that symptoms will subside. If the pain is severe, the recommended therapy for TNS is NSAIDs or oral opioid analgesic agents. The patient will be instructed to take ibuprofen 800mg every 8hrs for 3 days by

an anesthesiologist as long as the patient does not have any medical contraindications. On the third day, the patient will be called by the anesthesiologists to determine if symptoms are improving.

Discharge of the patient

All the routine standard of care recommendations followed in our hospital will be maintained during the discharge of the patients' home. A blinded (discharge) anesthesiologist who has not been part of the clinical care for the patient will conduct the discharge procedure.

Questionnaire Used to Evaluate Transient Neurologic Symptoms after Operation

1. If 0 is no pain and 10 the worst pain imaginable, how would you rate your pain after surgery? Buttock pain?

2. Did you have discomfort anywhere other than the surgical site? YES or NO? If Yes, where?

3. Did you have back pain after surgery? YES or NO (If no, go to 10) If Yes, (go to 4)

4. If 0 is no pain and 10 the worst pain imaginable, how would you rate your back pain?

5. Where was the pain in your back?

6. Did the pain radiate anywhere? YES or NO. Hips R L Both; Buttocks R L Both; Thighs R L Both; Calves R L Both; Sacrum R L Both

7. How long did the pain last?

8. Did the pain prevent you from sleeping, sitting, lying down, walking, going to work? Circle.

9. Had you ever had back problems or similar sensations before this surgery? YES or NO?

10. Is the pain medication prescribed to you helping with your surgical pain? YES or NO? (if no; advice patient to call the surgeon's office for alternate options for pain control)

Data to be collected

Surgery Time (min)
Intraoperative IV fluid (ml)- Goal <1000ml
Bladder volume (upon arrival to PACU)
Voiding time (min) Bupivacaine
Voiding time (min) Chloroprocaine
Return of Motor function (Bupivacaine vs. Chloroprocaine)
Return of Sensory function (Bupivacaine vs. Chloroprocaine)
Time to Ambulation (Bupivacaine vs. Chloroprocaine)
Discharge time (Bupivacaine vs. Chloroprocaine)
Evidence of Transient Neurological Symptoms (TNS)

Power and sample size considerations

In this study, the primary endpoint of the study "discharge time" is defined as the time when the patients are "fit to discharge" from the PACU. According to our clinical audit, patients who have received bupivacaine as part of their spinal anesthesia are "fit to discharge" after 240±90 minutes (4hours) stay in the PACU. For this study, we assume that the use of 2-Chloroprocaine will result in a clinically significant 30% reduction in the discharge time.[14] Sample size calculation for this study is based on these assumptions; a two-sided type –I error of 0.05, power of 80% and the proportion of patients ready to be " fit to discharge" (within the pre-specified discharge time described above) will be 70% and 40% in the 2- chloroprocaine group and the bupivacaine group respectively. The sample size required based on the above assumptions are 46 patients in each group a total of 92 patients. Additionally, we will increase the sample size to an additional 10% to accommodate for voiding difficulties due to unknown reasons. Finally to accommodate for any missing and early drop-outs we plan to enroll 55 patients in each study groups, a total of 110 patients will be recruited for this study.

Data analysis plan

Descriptive statistics will be used to report demographic and clinical characteristics (age, gender, type of surgery, medications, ASA status, comorbidities). Continuous data points will be analyzed using Student's t-tests or Wilcoxon rank-sum tests (depending on the distribution of the data) and chi-square or Fisher's exact tests for categorical variables. The time "fit to discharge" will be analyzed using Kaplan–Meier curves. Additionally, data will be analyzed using a multivariable Cox proportional hazards models adjusting for potential covariates. Also, the proportion of patients with trouble in voiding and required assistance in voiding urine in the PACU will be compared between the two groups.

Randomization

Patients will be randomly assigned to one of the two groups in a 1:1 ratio. The research office will provide sealed envelopes with randomization allocation. On the day of surgery, the research assistant will hand an enclosed envelope to the anesthesiologists performing the spinal anesthesia with the name of local anesthetic to use. On medical record, the group assignments will be recorded as a "study drug." The key to the randomization code will be stored in the research office. In the case of emergency PI and other clinical members will be provided with the allocation information. The PI or the designee will inform the IRB and the DSMB regarding unblinding the code. The date, time and reason for breaking the blind will be recorded in the source document and will be entered in the appropriate section of CRF.

Data Safety Monitoring Board (DSMB)

Data safety monitoring board will be comprised of an anesthesiologist and a surgeon. All unanticipated serious adverse events will be reported to the DSMB. In the event of unanticipated serious adverse events, a continuation of the study will be at the discretion of DSMB and IRB. Periodic DSMB meetings will evaluate the occurrence of any study-related adverse events.

Data Management

All study data will be collected and entered into the computer database. Each subject will be assigned to a random number code, and the key linking the code and the subject identifier will be stored in a locked cabinet. The computer database will be password protected and will be kept on the Montefiore

drive. The research manager is responsible for auditing the consistency of the data transcribed from the paper CRF to the computer. A protocol violation log will be maintained, and all protocol violations will be reported to the IRB and DSMB. The planned interim analysis (halfway through the recruitment) will be mainly focused on the adverse events, rather than the efficacy of the procedure.

Human safety

Spinal anesthesia carries the risk of bleeding, infection, delayed ambulation, pain after block regression (back pain or TNS) and risk of urinary retention. Furthermore, local anesthetics, which are routinely used for spinal anesthesia, carry the risk of local anesthetic toxicity, neurotoxicity, and allergic reactions. However, the right choice of local anesthetic may prevent any side effects allowing for successful spinal anesthesia in improving overall patient satisfaction and time of discharge from the outpatient setting.

In the past, long-acting local anesthetics such as hyperbaric bupivacaine, tetracaine, and levobupivacaine were injected intrathecally which resulted in delays in hospital discharge, prolong motor and sensory blockade and an increase in urinary retention. However, in recent years short-acting local anesthetics such as 1% chloroprocaine HCl, prilocaine, and mepivacaine are been used for ambulatory spinal anesthesia because of their fast onset, satisfying block, quick recovery, and minimal side effects.

In early production, sodium bisulfite was added as a preservative to chloroprocaine, which was set to be the cause of several cases of transient neurologic symptoms in patients that had intrathecal dosing. In recent productions, all preservatives and antioxidants have been removed from two of the three currently available preparations of CP. Preservative-free 2-chloroprocaine has been used in several retrospective and prospective studies, and there has been no evidence of an increase in neurotoxicity or TNS.[6-8] With the new FDA approved use of 1% Chloroprocaine for spinal anesthesia, it is expected that there will be more research studies on the cost-effectiveness, safety profile, and practicality of using this drug for short surgical procedures.

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