Title: Comparison of obturator nerve blockade and neuromuscular blockade for the prevention of adductor spasm in patients undergoing transurethral resection of bladder tumors.

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Protocol

1. Project Title:

Comparison of obturator nerve blockade and neuromuscular blockade for the prevention of adductor spasm in patients undergoing transurethral resection of bladder tumors.

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3. Abstract:

Transurethral resection of bladder tumor(s) (TURBT) is a commonly performed procedure to diagnose and treat bladder cancer. The obturator nerve is located lateral to the bladder wall in the pelvis prior to innervating the adductor muscles of the thigh. The adductor muscles include the adductor longus, adductor brevis, adductor magnus, and the pectineus muscle. These muscles are innervated by the obturator nerve and the adductor magnus muscle receives additional innervation from the tibial nerve [1]. In addition to hip adduction, these muscles contribute to flexion/extension as well as internal and external rotation of the hip [1].

Depending on the location of the tumor(s), electrocautery or surgical stimulation may result in stimulation of the obturator nerve, resulting in adduction of the leg, which is called the adductor reflex or spasm. This may occur violently and unexpectedly, and result in bladder perforation, bleeding, or cancer dissemination [2].

Ultrasound-guided obturator nerve blockade has been advocated as a technique to minimize or ablate the obturator reflex [2-4] in patients receiving spinal or general anesthesia for TURBT. Quadriceps weakness secondary to peripheral nerve blocks has been associated with an increased risk of falls in the orthopedic population [5-8]. Although obturator nerve blockade (ONB) results in adductor weakness [9, 10], it is not

known if this results in an increased fall risk. Much of the anesthesiology literature on ONB is focused on patients undergoing knee surgery and, to our knowledge, no literature exist regarding the incidence of falls in patients receiving an ONB for TURBT.

To date, there are no prospective studies comparing the incidence of adductor spasm in patients undergoing general anesthesia with neuromuscular blocking agents versus obturator block. No major complications—including falls—have been reported with obturator nerve blocks. This may be a reflection of underutilization, lack of reporting, or simply a reflection of their use primarily in an orthopedic patient population whose mobility status is limited and closely observed.

4. Background:

Much of the available data on obturator blocks is taken from the orthopedic anesthesia literature on patients undergoing knee surgery. To date, there are no complications (including falls) related to obturator blocks reported in the literature. ONB is performed in patients undergoing TURBT to minimize or ablate the obturator reflex [2-4].

Ultrasound guided regional anesthetic techniques have a long record of safety and efficacy, and are commonly performed for patients undergoing surgery in both the outpatient and inpatient setting.

Neuromuscular blocking medications are commonly used to prevent patient movement under general anesthesia. Use of neuromuscular agents may result in postoperative weakness, which may lead to hypoxemia and airway obstruction, complaints of muscle weakness or fatigue, longer postanesthesia care unit stays, delays in tracheal extubation, increased risk of pulmonary aspiration, and atelectasis [11]. Additionally, adductor spasm has been reported despite the use of these medications [12, 13].

Furthermore, there is a study that suggests that use of an obturator nerve block in patients undergoing TURBT may prolong time to cancer recurrence in patients with superficial bladder tumors [14]. The obturator block results in a decreased incidence of adductor spasm, which allows for optimal surgical conditions and improved tumor resection [14]. The incidence of adductor spasm during TURBTs is currently unknown. While one study has estimated the incidence to be 16.5% [18], three others have reported it to be 40-55% [13, 19, 20] in patients with posterolateral bladder tumors.

Given the presence of the adverse events associated with use of neuromuscular blocking agents and the current lack of adverse events reported with the obturator block, we are interested in conducting an investigation comparing the two approaches in a prospective and randomized manner.

5. Specific Aims:

The primary objective will be to compare the incidence of adductor spasm (also known as the obturator reflex) during transurethral resection of posterolateral bladder tumors under general anesthesia.

Secondary objectives will include assessments of leg weakness and fall risks, as measured using a handheld dynamometer and the timed up and go (TUG) test, respectively. Adverse events related to the anesthetic and surgical techniques will also be recorded.

6. Research Plan:

Veterans diagnosed with posterolateral bladder tumors will be invited to participate in the study. After obtaining written informed consent, the veteran will be randomized to receive an ultrasound-guided obturator block or a neuromuscular blocking agent after the induction of general anesthesia in an attempt to block the obturator reflex during surgery. Both techniques are commonly performed and accepted techniques for the prevention of the obturator reflex.

Inclusion criteria

1. Patients ≥ 18 years of age undergoing TURBT for unilateral or bilateral posterolateral bladder tumors
2. Ability to understand and provide informed consent

Exclusion criteria

1. Patient refusal or inability to provide informed consent
2. True allergy, not sensitivity, to any of the following substances:
    a. Local anesthetics
    b. Propofol
    c. General anesthetic agents
3. Pregnancy
4. Severe hepatic impairment
5. Evidence of infection at or near the proposed needle insertion site
6. Any sensorimotor deficit of the lower extremity, whether acute or chronic, as determined by the PI
7. Inability to walk without assistance
8. Lower extremity joint replacement surgery in the preceding six months

Methods:

Research related procedures: Veterans (n=60) with be randomized to the obturator block or neuromuscular block arm upon enrollment, using randomized permutated blocks of six (GraphPad Software, Inc). The TUG test and dynamometer measurements will be obtained preoperatively and one hour postoperatively. Handheld dynamometers are commonly used to determine leg muscle strength and have been utilized in multiple recent nerve block studies and other clinical settings [7, 8, 15]. The TUG test requires the participant to stand from a seated position, walk ten feet, turn around, and return to a seated position. The test is free and available to all health care

providers (http://www.cdc.gov/steadi/index.html). It is a sensitive and specific tool for evaluating fall risk with excellent intra- and interrater reliability [16]. It is easily performed, does not require specialized equipment or training, and correlates well with other balance and gait measures [17]. Times ≥ 13.5 seconds are associated with an increased risk of falls [16, 17].

Once a potential study candidate provides consent to participate in the study, s/he will undergo a baseline TUG test and dynamometer measurements.

Planned statistical analyses

All analyses will be conducted in JMP Pro 12.0 (SAS Institute, Cary, NC). Categorical measures (e.g. block success) will be summarized as percentages (%). For continuous measures (e.g. TUG, dynamometer), normally distributed measures will be summarized as means and standard deviations, and non-normally distributed measures will be summarized as median with interquartile range. Differences in block success between groups will be examined with χ^2 tests. Differences in dynamometer measurements and TUG tests will be examined through t-tests, with transformation of outcomes as necessary to satisfy assumptions of the statistical test. $P < 0.05$ will be considered statistically significant.

Sample size justification

The target sample size for the proposed study is n=60 (n=30 per group). Power calculations were performed assuming 80% power and alpha=0.05. With n=60, our sample can detect a minimum 28% decrease is block success in the neuromuscular block group compared to the obturator block group, assuming a 97% success rate in the obturator block group. This sample size will also be able to detect a minimum group mean difference of 7.4 on the TUG (SD=10.0).

Obturator block group

Standard of care: After the induction of general anesthesia, the block will be performed on the side of the posterolateral bladder tumor(s). If a patient has bilateral posterolateral bladder tumors, bilateral blocks will be performed. A time out procedure will be performed confirming the patient's identity, the proposed surgical procedure, and laterality of the tumor(s) and block procedure(s). The patient's inguinal region will be cleansed with Chlorohexidine prep solution. A 21ga Pajunk SonoPlex needle will be advanced under ultrasound guidance and 20-30mL of 2% mepivacaine will be injected using an interfascial approach. All nerve blocks will be performed by Dr. José Soberón, who has expertise in ultrasound-guided regional anesthesia. Block time will be counted as the time from needle insertion until the completion of the injections. Any inadequate/failed blocks will be recorded. Unless clinically indicated, neuromuscular blocking agents will be avoided (with the exception of succinylcholine for tracheal intubation).

Neuromuscular block group

Standard of care: After the induction of general anesthesia, rocuronium (a neuromuscular blocking agent) will be administered intravenously in 5-10mg increments

titrated to a goal of 2/4 twitches. An obturator block will not be performed unless adductor spasm persists despite the administration of additional rocuronium.

Research related procedure: The incidence of block- and procedure-related adverse events, including the obturator reflex, will be recorded. In addition to clinical observation, a Nerve Integrity Monitor (Medtronic) will be used to detect adductor spasm using continuous electromyography. Adhesive skin (non-needle) electrodes will be placed on the thigh to objectively detect and record instances of adductor spasm.

Standard of care: Unless contraindicated, all patients will be extubated and transported to the post anesthesia care unit (PACU). The patients will then be discharged home or to a hospital room (per the surgical service).

Research related procedure: One hour after arrival to PACU or when discharge criteria are met (whichever comes first), repeat dynamometer measurements and TUG tests will be performed. Patients will be called 24-48 hours post procedure to inquire about falls or evidence of nerve injury, as well as patient satisfaction.

7. Possible Discomforts and Risks:

In addition to the risks of general anesthesia, veterans in the obturator block group may experience the following: nerve damage, intravascular injection of local anesthetic, cardiac arrest, seizure, bleeding/hematoma, infection, ineffective or failed block, pain at the injection site, or numbness or tingling (paresthesia). These events are rare and, to date, none of these complications have been reported in patients receiving an obturator block.

Because the obturator block will be performed after the induction of general anesthesia, the enrolees should not experience any discomfort during the block procedure.

8. Possible Benefits:

Because adductor spasm may interfere with tumor resection, performance of an obturator block or use of neuromuscular relaxing agents may block or ameliorate the reflex and allow for safer operating conditions and improved cancer removal. The efficacy and safety of one approach versus the other is not known. The results of this study may be used to guide clinical decisions for future patients undergoing TURBT or to conduct larger prospective studies.

9. Conflict of Interest:

None of the investigators have any relevant financial disclosures.

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