PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

Answer/Response:

Transversus Abdominis Plane (TAP) block is a useful tool in pain management after abdominal surgery. It is a regional nerve block that targets T6-L1 thoracolumbar nerves running in the plane between internal oblique and transversus abdominis muscle. It is shown to help with post-operative pain management, reducing pain scores and narcotic pain medication use, as well as promoting earlier return to activity and recovery.[1,2] TAP block became a very popular, safe, and effective therapeutic adjunct for many different abdominal surgeries ranging from obstetric procedures to general surgery procedures like colorectal surgery.[3,4] Furthermore, it is used in plastic surgery procedures such as Deep Inferior Epigastric Perforator (DIEP) free flap or Transverse Rectus Abdominis Myocutaneous (TRAM) flap, as they involve extensive amount of abdominal soft tissue incision. Previous studies have shown that TAP block in these procedures significantly reduce post-op pain and narcotic pain medication use.[5,6] More recently, Exparel (liposomal bupivacaine) has risen to spotlight for providing a longer, sustained local anesthesia. Various surgical disciplines have adopted this agent as part of their pain management protocol. However, there are no literatures that describe the effect of TAP block using Exparel for breast free flap population. We hypothesize that delivering TAP block with Exparel (vs. plain bupivacaine) will provide longer regional blocking effect, hence aiding in pain control and recovery postoperatively.

Objectives/Hypothesis

Answer/Response:

- We hypothesize that liposomal bupivacaine (Exparel) TAP block will provide longer pain control compared to plain bupivacaine TAP block in abdomen-based free flap breast.
- Primary outcome = post-op pain scores during hospitalization, post-op narcotic pain medication use during hospitalization, post-op narcotic pain medication use after discharge (within 30 days of discharge)
- Secondary outcome = Length of stay, Post-op nausea and vomiting (PONV)

Study Design: Biomedical

1. Will controls be used?

Answer/Response: Yes

►IF YES, explain the kind of controls to be used.

Answer/Response: Usual care, TAP block with plain bupivacaine

2. What is the study design?

Answer/Response: Randomized, single-blind control study

3. Does the study involve a placebo?

Answer/Response: No

Human Participants

Ages: _18 and older___
Sex: __**Female**__
Race: ___**Any**_

Subjects- see below

1. Provide target # of subjects (at all sites) needed to complete protocol.

Answer/Response:
100 participants

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

Answer/Response:
Minimal.
Once the patient consents to the study, it is unlikely that they will drop out or withdrawal afterwards given that this is part of a usual care pain management protocol. No extra follow up is required for patients and all the outcomes will be part of a usual post-op data that will be recorded in Epic.

3. How many subjects will be enrolled at all sites?

Answer/Response:
This is a single site study – enrollment at UVA only.

4. How many subjects will sign a consent form under this UVA protocol?

Answer/Response:
All participants (100)

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

Answer/Response:

- All female patients who are 18 years or older who will undergo unilateral or bilateral abdomen-based free flap breast reconstruction at UVA Medical Center from February 2021 to January 2024.

2. List the criteria for exclusion

- Answer/Response: Subjects with ages <18 years

- Allergy to local anesthetic
- Inability to tolerate usual postoperative pain management regimen (Tylenol, Toradol, and Oxycodone PRN) for any reason
- Subjects who cannot read or understand English
- Subjects who are pregnant (self-reported)

3. List any restrictions on use of other drugs or treatments.
Answer/Response: None

Statistical Considerations

1. Is stratification/randomization involved?
Answer/Response: Yes

►IF YES, describe the stratification/ randomization scheme.

Answer/Response:
Random number generator will be used to enroll a subject into control TAP vs. Exparel TAP block group after consent is obtained before surgery. Patients will be blinded to their TAP block method. Surgeons/PI/ study coordinators will not be blinded to randomization. Surgeons/ PI/ study coordinators will have access to the randomization scheme.

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVA Statistician. Insert name Answer/Response:
_____ UVA Investigational Drug Service (IDS)
__x___ Other*:* Specify Answer/Response: Study coordinator/ medical staff in plastic surgery clinic

2. What are the statistical considerations for the protocol?
Answer/Response:

- This is a randomized, prospective trial that examines the effectiveness of Exparel TAP block (mix of Exparel + plain bupivacaine) compared to plain bupivacaine TAP block at University of Virginia Medical Center between February 2021 and January 2024. Patient information will be kept confidential and all identifying information will be removed. Data collected will involve:
    - General Demographic Data: age, gender, race, ethnicity, medical and surgical history, psychiatric history, medications, drug, smoking, alcohol abuse, occupation
    - Type of Reconstructive Procedure: procedure type, laterality

- TAP block information: liposomal bupivacaine vs. plain bupivacaine
- Post-operative Narcotic Requirement: total mg of oral opioid use in postop period during hospitalization and immediate post-operative period (30 days after discharge).
- Post-operative Data: LOS, pain scores, PONV incidence
- Complications

3. Provide a justification for the sample size used in this protocol.

Answer/Response: The primary outcome variable used for sample size calculation is post-operative narcotic requirement. Since we are unsure of the exact standard deviation for the population in terms of narcotic requirement, but we do have a limited number of patients that will be available for the study, we used four different standard deviations to confirm that we would have enough patients for 80% power (alpha = 0.05) to detect a difference in groups. We believe that the estimate of the standard deviation is most likely in the 10 mg range, so having 50 patients in each group would allow us to detect a difference of 5.66 mg between groups at 80% power.

Sample sizes	Standard deviation	Alpha	Power	Difference that can be detected
50 50	1	0.05	80%	0.57 mg
50 50	5	0.05	80%	2.83 mg
50 50	10	0.05	80%	5.66 mg
50 50	15	0.05	80%	8.49 mg

4. What is your plan for primary variable analysis?

Answer/Response:

Univariate analysis with Alpha <0.05 considered significant, variables with p<0.1 will be included in multivariate analysis to control for potential confounding variables and attempt to determine independent factors associated with outcomes.

Primary outcomes will include post-op recovery data- pain scores and postop narcotic requirement (total mg of opioids) both during hospitalization and up to 30 days after discharge. Secondary outcomes will include LOS and incidence of PONV.

5. What is your plan for secondary variable analysis?
Answer/Response:
Secondary outcomes will include LOS and PONV.

Two-sample t-tests or Mann-Whitney U tests will be employed for secondary variable analysis.

Exploratory multivariate analysis will be employed to determine potential confounding variables and attempt to determine the focus for future studies to determine independent factors associated with various outcomes.

6. Have you been working with a statistician in designing this protocol?

Answer/Response: Yes

IF YES, what is their name?
Answer/Response: Wendy Novicoff

7. Will data from multiple sites be combined during analysis?
Answer/Response: No

Study Procedures-Biomedical Research

1. What will be done in this protocol?
Answer/Response:
Participants will either receive plain bupivacaine TAP block (control/ usual care) or Exparel TAP block mix (experimental/ mix of Exparel and plain bupivacaine). Post-op data will be recorded in Epic and will be analyzed.

All the subjects will be recruited in UVA plastic surgery clinic when qualifying patients come in for pre-operative visits.

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.
Answer/Response: N/A

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
(e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
Answer/Response: N/A

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
(e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)
Answer/Response: N/A

Bibliography

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5. Wheble GA, Tan EK, Turner M, Durrant CA, Heppell S. Surgeon-administered, intra-operative transversus abdominis plane block in autologous breast reconstruction: a UK hospital experience. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* 2013;66(12):1665-1670.
6. Hivelin M, Wyniecki A, Plaud B, Marty J, Lantieri L. Ultrasound-Guided Bilateral Transversus Abdominis Plane Block for Postoperative Analgesia after Breast Reconstruction by DIEP Flap. 2011;128(1):44-55.