Safety and Mechanism of Action of Energy-Based Devices for the Treatment of Urogynecologic Conditions

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Introduction:

- Use of energy administration to the vaginal canal has been increasing, but questions regarding safety, efficacy and mechanism of action remain.
- Submucosa cellular changes require that energy penetrates deep into the tissue without causing damage to the mucosal tissue.
- Ablative lasers (e.g., CO_2 and Er:YAG) impact the superficial mucosa, but not necessarily the deeper connective tissue layers (Figure 1).

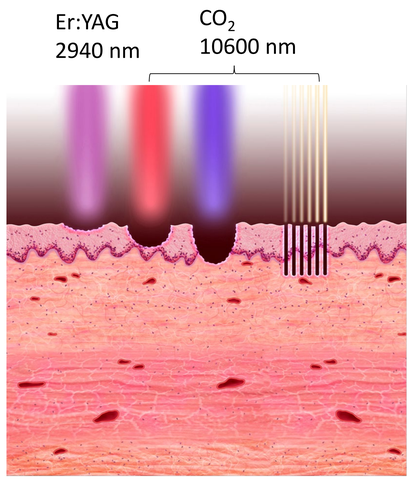
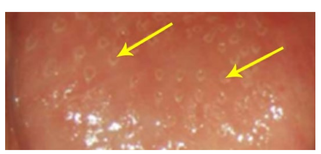
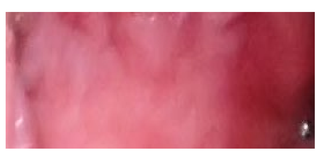


Figure 1: Deep of penetration through the vaginal tissue of different lasers.

- RF systems can penetrate deeper into the tissue due to **lower frequency and longer wavelengths** (compared to lasers).



Laser (tissue damage)
Arizona Institute of Urology



RF (healthy tissue)
Viveve

- Data indicate that cryogen-cooled monopolar radiofrequency (CMRF) treatment can elicit changes by volumetric heating deep in the tissue while being safe to patients.

Methods:

- Ovine ex vivo and in vivo studies were performed to investigate the depth of penetration and safety of CMRF treatment.
- ex vivo treatment was performed on isolated vaginal and peri-vaginal tissue at different regions of the vagina.
- In vivo, tissue was isolated following RF treatment and analyzed for tissue effects. Histopathology was used to evaluate the extent of treatment, cellular changes, and safety.
- Clinical outcomes were assessed in a practice setting & augment the preclinical safety data.

Pre-clinical Results:

- in vivo experiments with surgically impacted fluorotic probes confirmed that CRMF treatment results in volumetric heating throughout the lamina propria (Figure 2). These temperatures are associated with biological effects which align with positive clinical outcomes.

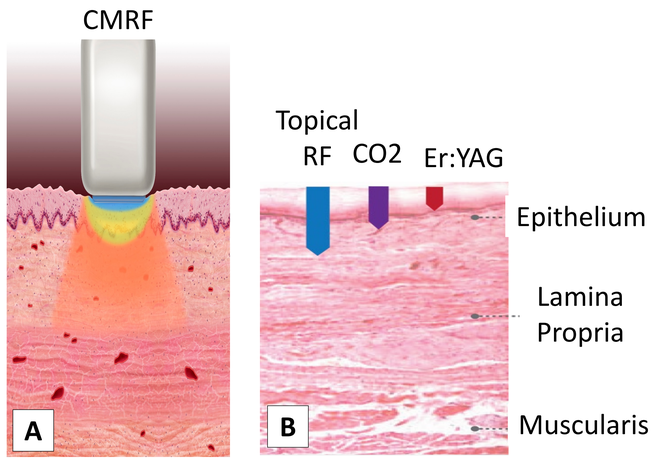


Figure 2: Vaginal penetration depth in A) CMRF and B) Other energy

Acknowledgements: Kathryn Husarek, PhD for data analysis and interpretation and Katya King for patient assessments.

Additional Information: For references and further information, please send inquiries to medicalaffairs@viveve.com and maria.canter.md@gmail.com

Pre-clinical Results:

- Histological analysis of ovine vaginal tissue demonstrate safety of CMRF Treatment (Figure 3).
  - No abnormalities observed
  - No increase in apoptosis at any treatment level
  - No impact on surrounding urethral/ rectal tissue

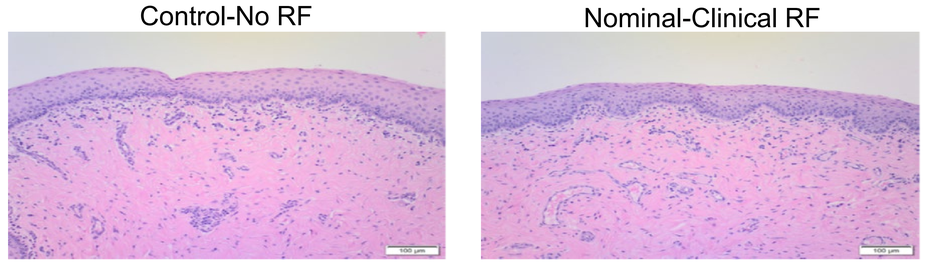


Figure 3: Vaginal and peri-vaginal tissues isolated from parous sheep treated with 3 different energy levels

Clinical Results:

- Viveve Treatments Dec2017 through Jul2018 (Tables 1 and 2)
  - Internally-developed treatment protocols
    - Stress Urinary Incontinence (SUI) = 220 pulses of CMRF
    - Sexual Function/ Vaginal Laxity = 110 pulses of CMRF
  - Assessment of SUI via Urogenital Distress Scale (UDI-6)
  - Follow-up time period of 3-6 months

Table 1: SUI Protocol

	IMPROVED	NO IMPROVEMENT	RESPONSE PENDING
PREMENOPAUSAL (n=5)	4	0	1
POSTMENOPAUSAL (n=8)	6	0	2

Table 2: Sexual Function/ Vaginal Laxity Protocol

	IMPROVED	NO IMPROVEMENT	RESPONSE PENDING
PREMENOPAUSAL (n=5)	2	2	1
POSTMENOPAUSAL (n=2)	2	0	0

Conclusions:

- The type of energy and mode of delivery will impact tissue penetration and the potential clinical benefits.
- CMRF energy affects the deeper connective tissue in the vaginal canal while protecting the mucosal tissues.
- Clinical practice data further support potential for CMRF treatment in urogynecological conditions.

Peer-reviewed materials on the Viveve device are included here.

Please note the following:

- In the United States, the Viveve System is indicated for use in general surgical procedures for electrocoagulation and hemostasis.
- FDA has not cleared the Viveve System as safe and effective for the uses described in the attached information.
- Some of the author(s) of these articles are employees of Viveve, or have a financial interest in the manufacturer or its products.
- There are no significant risks or safety concerns associated with the unapproved use(s) of the Viveve system that are known to Viveve, but not discussed in the attached documents.

Viveve Label: Viveve treatment tips: Instructions for Use

Symbols/Abbreviations

	Single Use only		Do not Re-sterilize
	Follow Instructions for Use		Do not use if packaging is damaged
REF	Reference Number	LOT	Lot number
STERILE EO	Sterilization by Ethylene Oxide		Legal Manufacturer
	Use by		Date of Manufacture
	Latex-Free	℞ ONLY	Prescription Only
	Separate Collection		DEHP Free
	Manufactured in U.S.A for: Viveve, Inc. Englewood, CO 80112 + 1 (720) 696-8100 www.viveve.com	EC REP	MedPass SAS 95 bis Boulevard Pereire 75017 Paris France

C0086

CAREFULLY READ ALL INSTRUCTIONS PRIOR TO USE. OBSERVE ALL WARNINGS AND PRECAUTIONS NOTED THROUGHOUT THESE INSTRUCTIONS. FAILURE TO DO SO MAY RESULT IN COMPLICATIONS.

The Viveve® System Technical User's Manual (TUM) is supplied as a separate document. The (TUM) contains detailed information describing the Viveve® System components, console set up, and guide to operation, maintenance, trouble shooting, and specifications. Please read the TUM prior to operation of the Viveve® System.

Description

The Viveve treatment tips contained in this package are a sterile single use component of the Viveve® System and designed to deliver radiofrequency (RF) energy from the Viveve console. The Viveve treatment tips can only be used in conjunction with the dedicated Viveve® System.

The following Instructions for Use (IFU) describe the use of the Viveve® System. Review instructions in the Viveve TUM carefully on how to set up the system, including the warnings and precautions. Read all manuals and instructions completely before using the Viveve® System or performing any procedures.

Indications for Use

The Viveve® System is indicated for use in General Surgical procedures for electrocoagulation and hemostasis.

Contraindications

The Viveve® System is contraindicated for use in patients with either an Implantable Pacemaker or an Automatic Implantable Cardioverter/Defribillator (AICD), or any other implantable electrical device, as they may be adversely affected by radio-frequency (RF) fields or current.

Storage Conditions

Store in a cool, dry place.

Warnings

- Never touch the treatment tip's electrode surface or allow the electrode surface to contact unintended tissue when RF power is being applied. Heating could occur to tissue below the surface resulting in protein denaturation of the subsurface tissue.
- Do not re-use the treatment tip. It is a single-patient-use item and is not intended for multiple patients. Reuse of the treatment tip can lead to failure and patient injury.

Viveve® System and Accessories

Model 88003

- Viveve Console, Catalog Number VIVGE01
- Viveve Handpiece, Catalog Number VIVHP01
- Viveve Footswitch, Catalog Number VIVFS01
- Viveve Return Cable, Catalog Number VIVRC01
- Viveve 5 cm Treatment Tip, Catalog Number VIVTT01

Model 88003S

- Viveve Console, S, Catalog Number VIVGE01S
- Viveve Handpiece, S, Catalog Number VIVHP01S
- Viveve Footswitch, Catalog Number VIVFS01
- Viveve Return Cable, Catalog Number VIVRC01
- Viveve 5 cm Treatment Tip, S, Catalog Number VIVTT01S

Accessories

- Viveve 8 cm Treatment Tip, Catalog Number VIVTT02
- Viveve Return Pad, Catalog Number VIVRP01
- Viveve Cryogen Canister, Catalog Number VIVCC01
- Viveve Coupling Fluid, Catalog Number VIVCF01
- Viveve Power Cords: United States, Canada, Mexico, Latin America, Thailand, Catalog Number VIVPC01

Procedural Instructions

1. Clean and prepare the treatment area and the surrounding surface with a non-alcohol based cleaner.
2. Confirm that the Viveve™ System, console with cooling Module, hand piece and footswitch (if used), is set up properly as described in the User Technical Manual.
3. The use and proper placement of the return pad is a key element in the safe and effective use of this device, particularly in the prevention of burns.
4. Apply the return pad onto a clean dry area of the skin of the patient near the designated area to be treated. Ensure the entire area of the return pad is in contact with the tissue.
5. Ensure that the treatment tip is fully connected with the handpiece before using.
6. Coupling fluid is applied to the treatment area and on the treatment tip regularly throughout the treatment to ensure good electrical contact with the treatment surface. Failure to have good electrical contact could affect the treatment outcome.
7. While ensuring that the treatment tip is in good contact with the treatment surface and confirming that the flashing blue light on the handpiece is illuminated, apply the RF energy to the target area by depressing the footswitch.
    a. The energy setting is 180 Joules.
    b. The energy density is 90 Joules/cm^2.
    c. Each energy application will treat a 1 cm x 2 cm area.
8. Repeat until treatment is complete.
    a. A total of five (5) passes are made in the treatment area.
    b. To ensure complete coverage, overlap the energy application by 50% or 0.5 cm^2.
    c. Apply additional Viveve coupling fluid during the treatment procedure.
9. After treatment is complete:
    a. The patient and her healthcare professional should have a conversation about when to resume certain activities based on the patient's medical history and tolerability during the procedure.
    b. The Viveve treatment tip must be disposed of properly in accordance with the applicable national/local/state environmental laws. Check local regulations for proper disposal of the treatment tip.