The American Journal of Surgery xxx (2017) 1–5

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Safety assessment of the use of ultrasonic energy in the proximity of the recurrent laryngeal nerve in a porcine model

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ARTICLE INFO

Article history:
Received 19 January 2017
Received in revised form
17 April 2017
Accepted 29 April 2017

Keywords:
Ultrasonic energy
Harmonic focus
Recurrent laryngeal nerve
Thermal damage
Energy devices

ABSTRACT

Background: Advanced bipolar and ultrasonic energy have demonstrated reduction of operating time and blood loss in thyroidectomy. However, these devices generate heat and thermal dispersion that may damage adjacent structures such as the recurrent laryngeal nerve (RLN). This study was designed to evaluate the safety profile of the Harmonic Focus+® (HF+) device through the evaluation of thermal injury to the RLN using different algorithms of distance and time with state of the art technology.

Methods: 25 Vietnamese pigs underwent activation of HF+ in the proximity of their RLN. They were divided into 4 groups according to activation distance (3 mm, 2 mm, 1 mm and on the RLN). Time of activation, time between tones of the ultrasonic generator, changes in the electromyographic signal using continuous nerve neuromonitoring, vocal fold mobility assessed by direct laryngoscopy and histological thermal damaged were evaluated.

Results: None of the pigs had loss of signal in the electromyography during the procedure; only one pig had isolated transient decrease in amplitude and one increase in latency. One pig had transient vocal fold paresis in the group with activation on the nerve. Evaluation of the nerves by histology and immunohistochemistry did not show significant changes attributed to thermal injury.

Conclusions: The use of ultrasonic energy close to the RLN is safe, provided that activation time does not exceed the necessary time to safely transect the tissue.

1. Introduction

Over the last 10 years, innovative hemostatic devices, such as advanced bipolar and ultrasonic energy (UE) have been developed and used in a variety of surgical procedures.[1] Particularly in the field of Endocrine Surgery, several studies have demonstrated that the use of UE significantly reduces surgical time and blood loss in patients undergoing thyroidectomy, without major adverse effects.[2–8] However, the potential of unintended thermal injury from energy devices to adjacent structures, especially the Recurrent Laryngeal Nerve (RLN) is still an important issue for many surgeons.

Animal studies have demonstrated that lateral thermal spread of one of the devices that use UE, the Harmonic Scalpel (HS), was between 1.6 and 2.4 mm[9] when it was used in arteries of pigs, and between 0.9 and 1 mm[10] when it was assessed in sciatic nerves of rats. Therefore, it has been recommended to avoid the use of UE $\leq$ 3 mm from peripheral nerve structures.[11]

One of the factors that have demonstrated to affect lateral thermal damage of energy devices is the time of activation.[12] In order to limit the time of activation exclusively to the time needed for vessel sealing, a new version of the HS, the HARMONIC FOCUS®+ (HF+) (Ethicon Inc. Cincinnati, OH) was developed. The generator of this device (G-11) has built in an adaptive tissue technology that provides the user an audible feedback tone change when minimal tissue remains between the blades and detects rapid increase in shears temperature. This technology provides reduction in power output to limit thermal spread and tissue damage.[12,13]

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http://dx.doi.org/10.1016/j.amjsurg.2017.04.013
0002-9610/

The present study was designed to define patterns of safety of the HF + when working in the proximity of the RLN in a porcine model. The aim of the study was to evaluate how different algorithms of distance and time produce thermal injury to the RLN and the recovery rate of nerve injury due to thermal damage.

2. Materials and methods

A group of 25 Vietnamese piglets, weighing between 30 and 60 kg, were included in the study. In all animals the HF+ was activated in power level 5 in the proximity to the RLN at different distances. Activation was performed when transecting soft tissue of approximately 2 mm in a dry field, close to the entrance of the RLN into the larynx. Piglets were divided into 4 experimental groups as follows:

- Group 1: (3 piglets) HF + activated at 3 mm from the RLN.
- Group 2: (3 piglets) HF + activated at 2 mm from the RLN.
- Group 3: (7 piglets) HF + activated at 1 mm from the RLN.
- Group 4: (12 piglets) HF + activated with the non-active blade in direct contact to the RLN.

2.1. Surgical technique

Pigs were fasted for a period of 12 h. General anesthesia was induced with no neuromuscular blockade. Pigs were positioned in a prone position. A preoperative laryngoscopy was performed and pigs were intubated with a 6.0 mm NIM Contact™ EMG endotracheal tube (Medtronic, Jacksonville, FL, USA) under direct fiberscope guidance.

Piglets were then rotated to a supine position in the operating table. A vertical cervical incision was performed. The strap muscles were divided with a monopolar electrocautery. Both the thymus and the thyroid were identified and retracted medially. The carotid sheath was opened and a 2 mm vagal Automatic periodic stimulation (APS) electrode was placed around the vagus nerve and connected to the NIM® Response 3.0 System (Medtronic, Jacksonville, FL, USA). The ipsilateral RLN was visually identified and confirmed with a Stimulator Probe. A 2 mm wide fragment of areolar tissue was dissected in the vicinity of the entrance of the RLN into the larynx. The HF+ was activated at the assigned distance. Activation of the device ended when the EMG showed loss of signal or when the tissue between the blades was completely transected. The skin incision was closed with absorbable sutures in a standard fashion.

2.2. Methods of evaluation

- Continuous Intraoperative neuromonitoring (C-IONM): All piglets underwent C-IONM on the vagus nerve, with 1 mAmp stimulation every 6 s. Laryngeal electromyography (EMG) was recorded throughout all the experiment and was extended in the presence of abnormal signal, until the altered signal recovered or up to 1 h.
- Vocal fold mobility: A certified Otolaryngologist blindly assessed vocal fold mobility in all animals under direct laryngoscopy using a flexible fiber optic laryngoscope at 3 different times: before surgery, 2 h, and 2 days after surgery. In the absence of vocal fold paralysis in the laryngoscopy 2 h and 2 days after surgery, the diagnosis of no vocal fold paralysis was established and no additional laryngoscopies were performed. In the presence of vocal fold paralysis in the laryngoscopy 2 days after surgery, the diagnosis of vocal fold paralysis was established and subsequent laryngoscopies were scheduled until recovery at 2 weeks, 1, 2, 4, and 6 months. In the event of vocal fold paralysis recovery, the diagnosis of transient vocal fold paralysis was established, the time for recovery was recorded and no additional laryngoscopies were performed. If vocal fold paralysis persisted at 6 months, the diagnosis of permanent vocal fold paralysis was established and the follow-up were finished.
- Histological/Immunohistochemical evaluation: In piglets of group 4, in the absence of vocal fold dysmotility, both nerves were harvested for histological examination, right after the laryngoscopy performed 2 days after surgery. Histological damage was analyzed by the morphological changes through the use of hematoxylin-eosin staining (H-E) and immunohistochemistry using the β Amyloid Precursor Protein (β-APP). An experienced pathologist performed blindly this histological analysis.

2.3. Operational definitions

The following variables were recorded and analyzed:

- Clinical: 1) Total time of HF + activation in seconds using an electronic chronometer, 2) Time between the change of tones of the G-11 generator in seconds using an electronic chronometer.
- C-IONM: 1) Basal and final amplitude and latency, 2) Presence and time of decrease ≥50% of basal amplitude, 3) Presence and time of increase ≥10% of basal latency, 4) Loss of signal (LOS) of EMG, defined as loss of depolarization waveform on the monitor screen or an amplitude <100 μVol under stimulation. Amplitude is correlated with the number of muscle fibers participating in the polarization during standard laryngeal EMG and corresponds to the magnitude of the EMG wave measured in microvolts (μVol). Latency symbolizes the speed of depolarization of the nerve fibers. It depends on the distance from the stimulation point to the ipsilateral vocal cord and is measured in milliseconds (mS).
- Fibroscopic laryngoscopy: 1) Vocal fold paresis, defined as the partial interruption of nerve impulse, resulting in weak or abnormal motion of laryngeal muscles and abnormal vocal fold movement, or 2) Vocal fold paralysis, defined as the total interruption of nerve impulse, resulting in no vocal fold movement.[14]
- Histology/Immunohistochemistry: Morphologic evaluation with H-E, analyzing: a) Dilatation of axons, b) Nerve edema, c) Perineural inflammation, and 4) Presence of basophilic deposits was performed. Nerves were stained with β-APP Immunohistochemistry and were subjectively classified as mild (+), moderate (++), and severe (+++) according to the intensity of nerve stain.

Our institutional ethical committee for animal studies approved the protocol. Microsoft Excel for Mac 12.2.6 and IBM® SPSS® Statistics version 20.0 (IBM Inc. Chicago, IL) were employed for the statistical analysis. Data was descriptively expressed as mean ± standard deviation (SD) with range values whenever a normal distribution was observed. Non-parametric descriptive measures were used whenever a variable distribution was not Gaussian. Univariate analysis was used for individual variables depending upon the intrinsic variable scaling; whereas bivariate analysis was performed to assess potential statistical associations or correlations. Mann-Whitney *U* test and Kruskal-Wallis one-way analysis of variance were used for the analysis of continuous variables. For categorical variables, R x C tables was employed using Fisher's exact test in all statistical contrasts. Any *p* value equal or less than *0.05* or *5%* (type I error) was considered statistically

Please cite this article in press as: Chávez KV, et al., Safety assessment of the use of ultrasonic energy in the proximity of the recurrent laryngeal nerve in a porcine model, The American Journal of Surgery (2017), http://dx.doi.org/10.1016/j.amjsurg.2017.04.013