Cover Page

OFFICIAL TITLE OF THE STUDY:

Ability of the Analgesia Nociception Index monitor to distinguish between excessive analgesia and inadvertent parasympathetic nerve stimulation during surgery of large cerebellopontine angle tumors

BRIEF TITLE:

ANI Parasympathetic monitoring in neurosurgery

STUDY ID: DC 2015/143

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AIM OF THE STUDY

To determine the Ability of the Analgesia Nociception Index monitor in distinguishing between excessive analgesia and inadvertent parasympathetic nerve stimulation during surgery of large cerebellopontine angle tumors

PROTOCOL

Background

The cerebellopontine angle (CPA) is an inverted triangular cisternal space within the posterior fossa bounded by the petrous temporal bone laterally, the cerebellum and pons medially and the lower cranial nerves (CN IX: glossopharyngeal, X: parasympathetic (pΣ) and XI: accessory) inferiorly (fig.1).[1] Surgery of large CPA tumors (>2 x 2 cm diameter), with compression of the pons exposes the patient to inadvertent pΣ nerve stimulation (IPNS) leading to bradycardia and asystole.[2] The analgesia nociception index monitor (ANI™, Metrodoloris, France) detects the pΣ tone based on the interaction between the respiratory cycle and heart rate variability (HRV).[3] The device uses a wavelet-based algorithm to provide an index ranging from 0 (minimal pΣ tone, maximal stress level and nociception) to 100 (maximal pΣ tone, low stress level and analgesia) with a value of 50 being considered by the manufacturer as the cut-off. High ANI values (>70) are generally attributed to opioid overdose. [4] In a pilot study, the investigators previously demonstrated a shift to high ANI values (> 90) induced by IPNS.[5] Despite the abundant clinical reports about this index, to the knowledge of the investigators, only a few studies have been published in the neurosurgical setting.[6, 7]

The aim of this study was to assess the ANI monitor's ability to distinguish between excessive analgesia and IPNS during surgery of large CPA tumors.

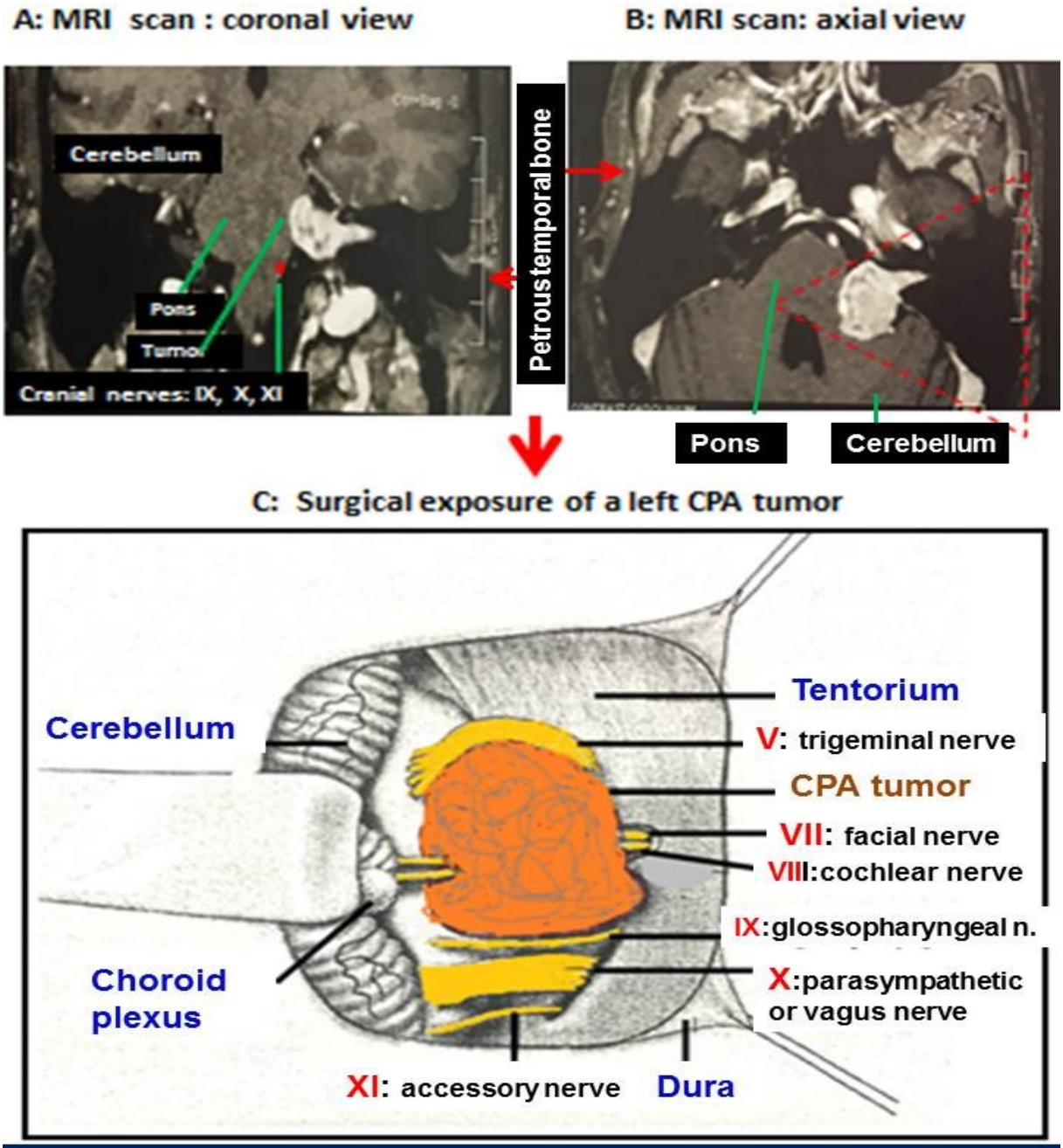


Fig.1: Anatomical landmarks of a large cerebellopontine angle tumor

Study design

This prospective observational study was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, study identifier: DC 2015/143) and performed between November 2015 and November 2017. After written informed consent was obtained, 75, ASA physical status II-III, participants undergoing surgery of large CPA tumors were included. Exclusion criteria were age below 18yr, pregnant women, arrhythmia, preoperative use of vagolytics, β-blockers and clonidine.

Anesthetic technique

The participants fasted for 6 h and were premedicated with oral hydroxyzine 1 mg kg^{-1} 1 h before induction of anesthesia. After arrival in the operating room, standard monitoring included a five-lead ECG, pulse oximetry (spo2), non-invasive arterial pressure (General Electrics, Helsinki, Finland) and an intravenous line was placed at the forearm or hand of the patient. An EEG sensor was then placed at the partipant's forehead to calculate the bispectral index (BIS) for the continuous assessment of the depth of anesthesia (Aspect A-2000 XP™ version 3.31, Aspect Medical systems, Newton, MA, USA). The ANI monitor (PhysioDoloris monitor; Metrodoloris™, Lille, France) was connected to the ECG analogue output of the anesthesia monitor (GE-Healthcare™, Helsinki, Finland) for online extraction of the ECG signal and calculation of two ANI values: instantaneous (ANIi) and mean (ANIm) based on a 4 min moving average period.

Anesthesia was performed by anesthesiologists and nurse anesthesists not involved in data analysis. Target-controlled total intravenous anesthesia (Orchestra® Base Primea, Fresenius Kabi™, France) was done with propofol (Schnider model site-effect concentration: 4-6µg/mL) guided by a BIS of 30-40 and Remifentanil (Minto model site-effect concentration:

4-6ng/mL) guided by an ANIi between 50-70. A 0.5 to 1 point increment or decrement of the effect site concentration was allowed, at a time, with regard to the set anesthesia objectives. No neuromuscular blocking drug was used throughout the perioperative period. After tracheal intubation, ventilation was started at a rate of 12 cycles per min and tidal volume was adjusted in order to maintain the end-tidal CO2 between 30 and 45 mmHg

Primary Outcome Measures:

1. Differences in ANIi values during bradycardia versus when Remifentanil effect size concentration >6ng/mL. ANI, HR and Remifentanil effect site concentration were continuously recorded with event markers on the ANI monitor at the onset of bradycardia (HR<45 bpm) or Remifentanil effect site concentration>6ng/mL

   Time Frame: ANIi values recorded at Day 1 only during surgery (duration: 4-6 hours)

2. Differences in the area under the ROC curves between ANI values for IPNS and excessive analgesia. ROC curves were built at different ANIi for IPNS or EA

   Time Frame: ANIi values recorded at Day 1 only during surgery (duration: 4-6 hours)

Secondary Outcome Measures:

3. The percentages of IPNS and EA cases

   The percentages of IPNS or EA cases on the overall study population were calculated.

   Time Frame: Cases observed at Day 1 only during surgery (duration: 4-6 hours)]

Statistical Analysis Plan

A sample size of 65 patients was calculated based on our pilot study which detected 18% of IPNS cases with an α-error of 0.05 and 90% Power.[8] The changes in ANIi and HR triggered by intraoperative events were compared using paired t-tests and McNemar's test. Receiver-operating characteristic (ROC) curve was built at different ANIi points. The 95% confidence interval of the area under the curve (AUC) was calculated using the bootstrapping method (1000 iterations). The best cut-off ANI points (sensitivity close to specificity) for IPNS and EA were compared in order to test the ANI monitor's ability to distinguish between these two events. The good diagnostic performance of the monitor was defined as an AUC $\geq$ 0.8. The closer both sensitivity and specificity are to 1 at the same time, the better the performance. [9] For all analysis, a p value <0.05 was considered significant. Statistical analysis was performed using MedCalc Statistical Software version 18.11.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019)

Results

Sixty nine participants (ASA 1-3, mean age: 53 ± 13 yr, body mass index: 23.9 ± 3.6 kg/m^2, male/female ratio: 36/33) with large CPA tumors were included. Two were excluded because of incomplete data.

The mean duration of surgery: 5.5 ± 1.2 h with mean consumption of propofol (3.3 ± 1.0 g) and remifentanil (3.6 ± 1.5 mg).

Twelve cases of IPNS were observed with sudden bradycardia terminating in asystole in 4 of them. An abrupt increase in ANIi was observed before bradycardia in these participants.

Excessive analgesia (Remifentanil site effect > 6 ng/mL) was observed in 7 cases with no significant change in heart rate (fig.2)

The AUC of EA was significantly higher than the AUC of IPNS (fig.3).

The best cut-off value of ANIi for excessive analgesia was ANIi >82 with a sensitivity of 85% (95% CI: 42-99%) and specificity 82% (95%CI: 70-90). The best cut-off value of ANIi for IPNS was ANIi >88 with a sensitivity of 100% (95% CI: 74-100%) and specificity 96% (95%CI: 88-100).

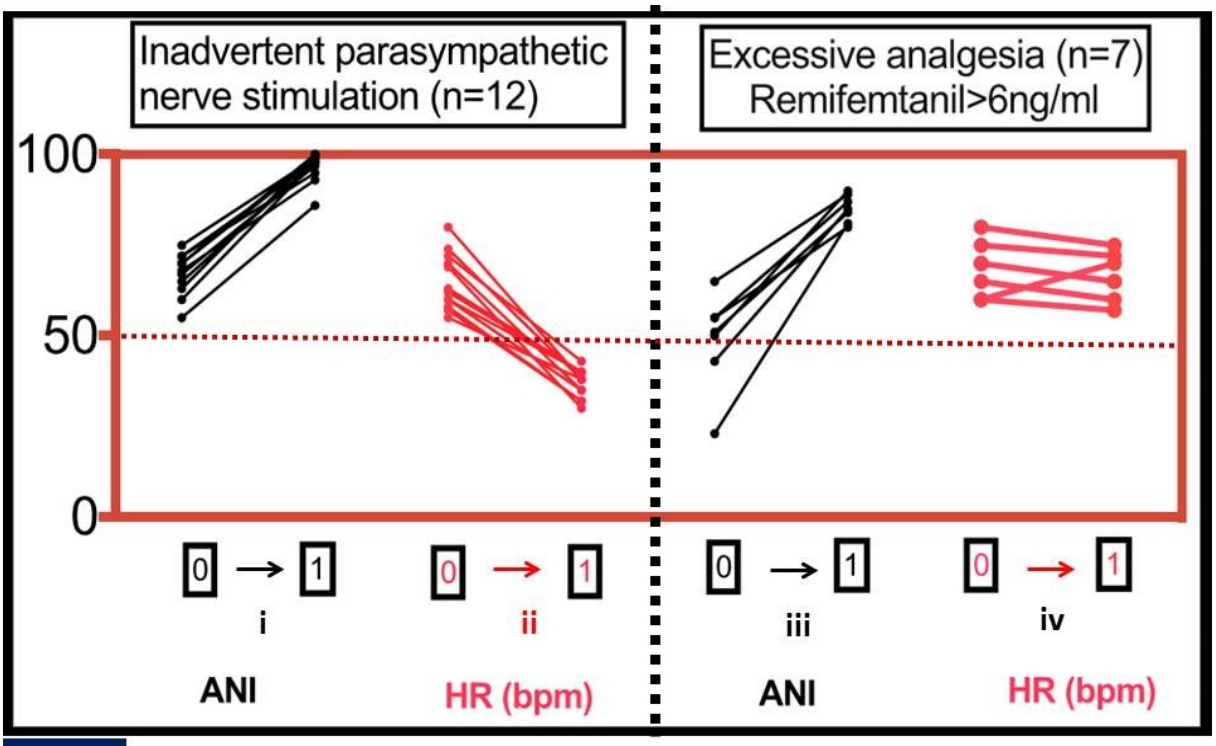
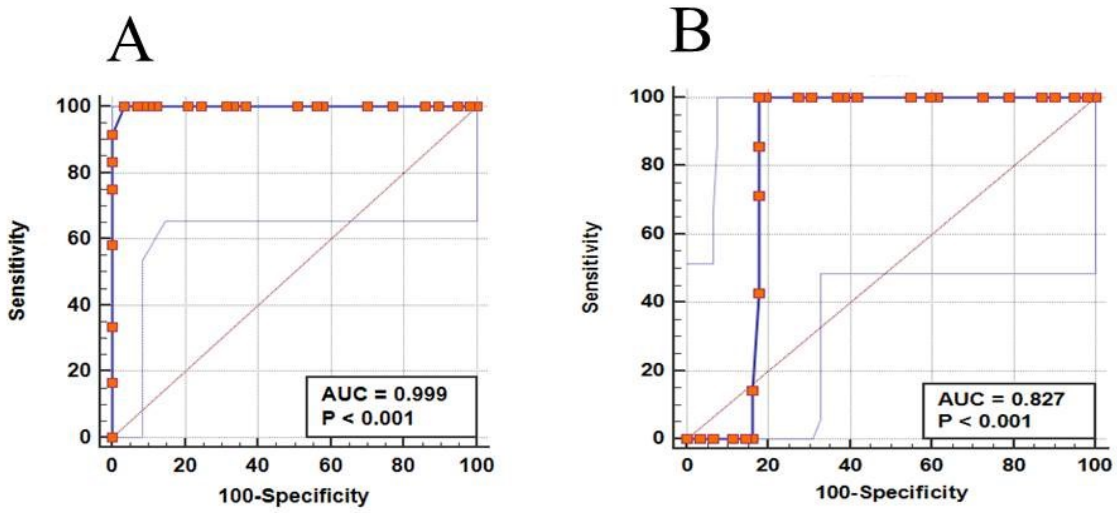


Fig.2 Legend: **0** (within 1 min before) and **1** (within 1 min after)

i: p<0.0001 ii: p<0.0001 i: p=0.0002 ii: p=0.31



AUC: area under the curve

ROC curves generated for excessive analgesia (A) and inadvertent parasympathetic nerve stimulation (B)

The AUC of A vs B (P = 0.0003)

Fig.3

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