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Support of Acute Pain Therapy by Analgesia Nociception Index in Post Anesthesia Care Unit: A Randomized Controlled Trial

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Abstract

Objective: Postoperative pain management requires a well-directed pain therapy. Generally, the assessment of pain intensity depends on a self-evaluated numeric rating scale (NRS, 0 to 10). Recently, a pain monitor using a so-called "ANI" (analgesia nociception index; 100 to 0) was introduced. The higher the ANI, the lower the pain intensity is considered. The aim of this study was to investigate if the use of ANI improves acute pain therapy in the post anesthesia care unit (PACU) by means of the experienced pain intensity (mean NRS) as the primary outcome parameter.

Methods: After admission to PACU, patients were randomly assigned to the "supported by technique" (TC) or the "control group" (CO). In both groups, self-assessment of pain intensity was requested every 15 minutes and pain therapy was provided according to internal clinical standards when the self-reported NRS by the patient exceeded 4. In the TC group, NRS pain score was additionally assessed when ANI fell below 50.

Results: Out of 91 collectively included patients, 46 were assigned to the TC group. The mean NRS did not differ between the groups (p=0.192) at discharge. However, suitability of the ANI monitor was strongly dependent from the individual patient. In some patients, a strong negative correlation was obtained, in other patients no correlation or, curiously, a strong positive correlation was observed.

Conclusion: Although objective pain intensity assessment would be beneficial for postoperative care, its measurement remains challenging.

Keywords: Pain; Analgesia; Pain management; Postoperative pain; Analgesia nociception index; Heart rate variability; Pain monitoring

Introduction

Despite an increased understanding of its management, postoperative pain remains a relevant challenge [1]. Several studies suggest that postoperative pain is managed inadequately and is considered to be not satisfying for nearly 50% of patients [2]. But, sufficient pain management is important to reduce morbidity and mortality [3,4]. Generally, pain management is based on patient's self-evaluation. Therefore, a number of scoring systems are available [5]. The numeric rating scale (NRS) is one of the most frequently used tools for assessing pain. Here, patients evaluate their pain using a rating scale, ranging from 0="no pain" to 10="worst pain intensity" [6]. Individuals with communication impairment are not able to rate their pain intensity. Although recent findings suggest that the Non-Verbal Pain Scale Revised (NVPS-R) and the Critical Care Pain Observation Tool (CPOT) are able to detect pain in PACU patients [7], a "pain monitor", providing an objective pain measurement is desirable. A "pain monitor" may improve pain therapy in a number of ways, e.g., by having the ability to "predict" pain perception and thus may enable clinicians to act pre-emptively. In the last decades, diverse technical approaches were investigated [8,9] like the Med-Storm Pain Monitor (Med-Storm Innovation AS, Oslo, Norway), which calculates the number of fluctuations of skin conductance (NFSC) as a measure for pain intensity [10]. But, clinical trials led to inconclusive results. Besides, determined correlation between the NRS and the NFSC was weak [11]. Recently, the "ANI monitor" (Metro Doloris, Lille, France), measuring the analgesia nociception index (ANI), was introduced. The ANI, ranging between 0 and 100, is based on heart rate variability (HRV) derived from electrocardiogram (ECG) data [12]. Low ANI values reflect a low parasympathetic prevalence and high values reflect a high one [12,13]. This means that the higher the ANI, the lower the pain intensity is considered. In awake patients, target values between 50 and 100 should be aspired.

We hypothesized that a continuous pain monitoring in postoperative awake patients using the "ANI monitor" can improve pain therapy. The primary outcome parameter of this randomized, controlled, single-blind trial was the mean NRS. Secondary endpoints were the number of pain occurrences, the duration of stay in the post anesthesia care unit (PACU) and the total dose of administered opioids.

Methodology

Ethical approval for this study (EK 041/14) was provided by the local ethics committee (Ethics Committee at the RWTH Aachen Faculty of Medicine) and the study was registered at the German Clinical Trials Register (DRKS00006220) on July, 16th, 2014.

After written informed consent, patients with non-emergency surgery receiving general anesthesia were included in this randomized, controlled, single-blind trial from June 2014 to April 2016 at the University Hospital Aachen.

The inclusion criteria were: ability to give written consent, over 18 years of age, receiving general anesthesia, a "painful" surgery with a planned duration of at least 90 minutes and an intended postoperative stay at the PACU. Patients with implanted pace makers, cardioverter defibrillators, a heart transplant, a regional anesthesia, a patient-controlled analgesia (PCA), a planned stay at the intensive care unit (ICU), catecholamine therapy, atrial fibrillation, arrhythmias or bradypnoea were excluded.

After surgery, the patients were randomized into two groups: "supported by technique" (TC) or "control group" (CO) by block randomization. The randomization list was prepared by an independent person using Randlist V1.2 (Datinf GmbH, Tübingen, Germany). Closed numbered envelopes containing allocated group IDs were used that were opened by the investigator after the patient arrived at the PACU.

Patient monitoring and medical treatment followed internal standards and were identical in both groups. After admission to the PACU, the Philips IntelliVue MP30 monitor (Philips Electronics N.V., Amsterdam, Netherlands) and the ANI monitoring (Metro Doloris, Lille, France) were applied measuring heart rate, non-invasive blood pressure, average ANI measure and oxygen saturation. Additionally, NRS score (primary outcome parameter) as well as the number of pain occurrences, the duration of stay in the post anesthesia care unit (PACU) and the total dose of administered opioids (secondary outcome parameter) were assessed. To avoid patient-related influences on ANI assessment, measurements were documented before requesting a NRS score.

For data collection a standardized data sheet titled "admission to PACU" was filled out. Thereafter, data assessment was repeated every 15 minutes on the sheet "periodic data collection".

If a patient's NRS score or a pain occurrence indicated by the patient exceeded the threshold of NRS 4, pain therapy was performed according to internal hospital standards by an independent person who was not involved in the data collection. Usually, piritramide (0.05 to 0.1 mg kg^{-1}) combined with a non-opioid analgesic substance (metamizole and/or paracetamol), was administered. Pain treatment was recorded on an additional sheet called "reaction to acute pain." This sheet included vital signs, the NRS and ANI score, administered medication (if any) and effect of pain therapy after 5 minutes. In addition, exclusively in the TC group, patients were asked for the necessity of analgesics (indicated by a NRS >4) when the ANI score fell below 50. In the CO group, ANI measures were ignored.

Finally, before leaving the PACU, the sheet "discharge of PACU" was completed (Figure 1). The ANI measure was not visible for the patient in any case.

Prior to the study, a power analysis was performed using G*Power (G*Power, Duesseldorf, Germany) using an a-priori, two-tailed t-test with a predefined power of 0.8 and α=0.05. The effect size was assumed to be 0.5. The power analysis resulted in a number of 128 patients. Because of potential drop outs, the target size of patients to be included was set to 138.

All data was analyzed with SPSS Statistics 23 for Windows (SPSS Inc., IBM Business Analytics Software, Armonk, NY, USA). The collected data did not follow a normal distribution.

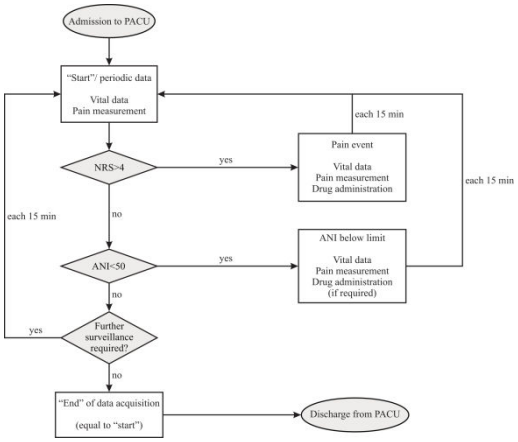

Figure 1: Flow chart of study protocol. After admission to the Post Anesthesia Care Unit (PACU), data acquisition started and was performed every 15 minutes, in case of occurring pain (NRS>4) and prior to discharge from the PACU. Only in the technically supported group, the Analgesia Nociception Index (ANI) measurement was considered and pain relief performed if necessary.

Therefore, median values and interquartile ranges were used. Spearman's test was used to calculate the correlation between the NRS and respective ANI for each patient individually. Subsequent correlations were divided into three categories, A, B and C. Patient data sets with a significant correlation (p-value below 0.05) were allocated to category A (negative correlation coefficient) or B (positive correlation coefficient). Patients showing no significant correlation were assigned to category C.

Mann-Whitney-U-Test was used to analyze differences between two independent groups (TC versus CO), the Wilcoxon Test was used for repetitive parameter assessment (PACU arrival and discharge) and the chi quadrat test was used to compare frequencies of pain occurrences and for subgroup analysis. The Receiver Operating Characteristic (ROC) curves were performed for analysing sensitivity and specificity to detect pain with intensities of NRS>2, NRS>4 and NRS>6 by means of ANI. For subgroup analysis, performed anesthesia (volatile anesthetics or total intravenous anesthesia), hypertonia, chronic pain disorders, nicotine abuse or sex were considered.

Results

In total, 138 patients were screened by studying the surgery schedule for the next day from June 2014 to April 2016 at the University Hospital Aachen. Out of these patients, 47 subjects were excluded. One patient did not meet the inclusion criteria, 8 patients declined to participate and 38 patients were excluded on the basis of "other reasons" such as an unexpected stay at intensive or intermediate care unit and changes in logistic processes.

Finally, 91 patients were randomized and analyzed from which 46 were allocated to the TC and 45 to the CO group after arrival at the PACU. After randomization, no losses or exclusions were registered.

Demographic	TC group (n=46)	CO group (n=45)
Sex; men	15	17
Age; years	56 (± 17.5)	55 (± 17.0)
Anaesthesia procedure: volatile anaesthetics	28	24
Type of surgery		
Trauma surgery	11	11
Orthopaedics	14	15
Ear, nose and throat surgery	5	10
Oral and maxillofacial surgery	2	3
Vascular surgery	1	1
Plastic surgery	2	2
Operative gynaecology	3	0
Neurosurgery	6	1
General surgery	0	1
Other	1	1

Table 1: Demographic and clinical data. Data are stated as mean and standard deviation or number.

After group allocation, the study groups showed similar characteristics with respect to sex, age and anesthesia procedure (Table 1). Upon arrival at the PACU, the NRS scores did not differ significantly between the TC and the CO group (5.0 (IQR 1.5-7.75) vs. 2.0 (IQR 0.0-6.0), p=0.051). During their stay in the PACU, no significant differences including the mean NRS, ANI and vital data were observed between the groups, as well as upon discharge from the PACU (Table 2).

Pain intensity decreased in the TC group during the stay in the PACU (5.0 (IQR 1.5-7.75) vs. 2 (IQR 1.0-3.25), p<0.001). In the CO group, the NRS score remained nearly constant (2.0 (IQR0.0-6.0) vs. 2.0 (IQR0.25-3.0), p=0.05) (Figure 2).

The ANI increased in both groups over the time period (53.0 (IQR 40.0-68.0) vs. 58.5 (IQR 52.0-74.25), p=0.002 in the TC group and 56.0 (IQR 42.5 - 67.5) vs. 62.0 (IQR 53.0-75.0), p=0.005 in the CO group).

The number of pain occurrences did not differ significantly (TC group: 90 episodes vs. CO group: 82 episodes; p=0.703). In TC group, the number of occurrence when ANI fell below 50 was 137. In 34 episodes (24,8%), opioid therapy was necessary. However, duration of PACU stay was prolonged in the TC group (96.5 min (IQR 70.5-132.0) vs. 70 min (IQR 56.5-113.5); p=0.013).

The number of mean total opioid dose (piritramide) did not differ (6.0 mg (IQR 3.0-9.0) vs. 6.0 mg (IQR 3.0-7.5); p=0.258) (Table 3).

Parameters	Arrival at PACU			Median values at PACU			Discharge from PACU		
	TC group	CO group	P value	TC group	CO group	P value	TC group	CO group	P value
NRS (Numeric Rating Score)	5 (1.5-7.75)	2.0 (0.0-6.0)	0.051	3.0 (2.0-5.0)	2.5 (1.0-3.5)	0.117	2.0 (1.0-3.25)	2.0 (0.25-3.0)	0.192
ANI (Analgesia Nociception Index)	53.0 (40.0-68.0)	56.0 (42.5-67.5)	0.606	58.0 (49.0-69.5)	62.0 (54.0-71.25)	0.351	58.5 (52.0-74.25)	62.0 (53.0-75.0)	0.525
Blood pressure systolic (mmHg)	128 (118-147)	126 (115-134)	0.313	125 (113-135)	123 (113-133)	0.997	119 (106-131)	122 (109-137)	0.404
Heart rate (beats/min)	79 (70-93)	76 (68-90)	0.497	75 (68-85)	72 (66-79)	0.177	77 (65-88)	70 (64-81)	0.103

Table 2: Primary endpoints and vital data in Post Anesthesia Care Unit (PACU) for the "supported by technique" (TC) and the "control group" (CO) are given for three time points. Data are stated as median values and interquartile ranges.

Some patients showed a negative correlation between NRS and ANI (subgroup A, n=11), others no correlation (subgroup C, n=65) or a positive correlation (subgroup B, n=4). In some case (n=11), observation period was too short to obtain enough data for correlation analysis.

Regarding subgroup analysis, neither the performed anesthesia procedure (p=0.535), chronic pain disorder (p=0.537), nicotine abuse (p=0.314), arterial hypertension (p=0.687) nor the sex (p=0.709) demonstrated a relation to the subgroups.

Related to the criterion ANI<50, sensitivity was 36.6 % and specificity was 76.2 % for the detection of NRS>4, 31.5% (76.4%) for NRS>2 and 38.3% (73.6%) for NRS>6 (Figure 3).

Discussion

In this study, we examined if a pain monitoring using the ANI monitor improves pain management in the PACU. Pain was adequately treated in both groups. The primary outcome parameter did not differ. However, PACU stay was longer in TC group. Interestingly, patient-individual correlations between the ANI and the NRS score varied

markedly and could be divided into three categories: moderate to strong negative correlation, moderate to strong positive (paradox) correlation or no correlation. Additionally, the ROC analysis for pain detection using an ANI threshold of <50 showed a low sensitivity and specificity for detection of NRS>2, NRS>4 and NRS>6.

However, due to the relatively small number of patients, these results should be considered with restraint.

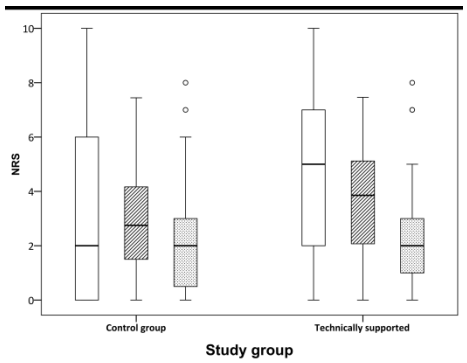

Figure 2: Boxplot of Numeric Rating Scale (NRS) values for the "control group" and technically supported group after admission to the Post Anesthesia Care Unit (PACU) (white box), during stay (striped) and just before discharge (dotted) from PACU.

Since there was no correlation between ANI and NRS score in most of our study patients (n=65), the application of the ANI monitor finally did not lead to an improved pain management.

But, several studies demonstrated a benefit using the ANI- monitor, even in pain assessment of critically ill patients [14]. Furthermore, a pilot study reported that ANI may assess acute procedural pain in children [15]. Other studies present the possibility to detect surgical stimuli or reflect various stimuli [16,17]. Additionally, Boselli et al. pointed out that postoperative ANI monitoring showed a negative correlation between the ANI and NRS at PACU arrival. Moreover, the ANI operated more reliable in patients who received propofol in contrast to patients who received a volatile agent [18]. In contrast to our study, Boselli et al. included patients with relatively strict inclusion criteria: ASA I-II patients who underwent surgical procedures like ear, nose and throat surgery, endoscopy and plastic surgery. In another study, Ledowski et al. pointed out, that ANI and NRS correlated only weakly [19]. Except for restraining to anesthesia procedures with volatile agents, preselection was less restrictive as compared to Boselli et al., so that thermoregulation, severe pain and volume state should be considered influence factors [19].

So, despite a similar study design, results differed. This fact was also discussed by the authors [20,21]. Boselli et al. indicate that the choice of intraoperative analgesia, the hypnotic agent and the duration of exposure to this may have an influence on the ANI [20]. Ledowski suggests that the postoperative pain level due to the surgical procedures was more varying in his study [21]. Additionally, a study in healthy male students pointed out that ANI does not measure pain exclusively, but may be affected by stress and emotion. Here, an unexpected and expected pain as well as an expected non painful and sham stimuli were administered in a random order [22].

To sum up, pain detection using the ANI monitor led to inconsistent results. Due to their influence on the autonomic nervous system and thus on the HRV, several factors affect ANI reliability.

Secondary endpoints	TC group	CO group	P value
Pain occurrences (times)	90	82	0.703
Duration of stay in PACU (min)	96.5 (70.5-132.0)	70.0 (56.5-113.5)	0.013
Mean total dose of administered opioids (mg)	6.0 (3.0-9.0)	6.0 (3.0-7.5)	0.258

Table 3: Secondary endpoints in Post Anesthesia Care Unit (PACU) are given for the "supported by technique" (TC) and the "control group" (CO). Data are stated as median values and interquartile ranges.

First, various patient-associated factors should be considered: study population (anesthetized, sedated or awake, children or adults, patients or volunteers), comorbidities and performed anesthesia procedure. Ogawa et al presented that volatile anesthesia led to a more significant reduction in sympathetic nervous modulation of peripheral vasculature than total intravenous anesthesia, even though cardiac baroreflex indices did not differ significantly [23].

Furthermore, Kanaya et al. showed that sevoflurane affects cardiac parasympathetic tone less as an induction of anesthesia with propofol [24]. Additionally, the duration of volatile anesthesia exposure affects the baroreflex control of heart rate [25,26].

Second, the setting and environment (clinical or laboratory) must be considered. Regarding the PACU, various stressors should be considered including anxiety, disorientation and noise.

Third, the type of surgery has an influence on the patient's volume status, thermoregulation and occurring pain.

In our study, a heterogeneous study population was included in terms of patient-associated factors and types of surgical procedures with a huge variety of drug therapy. Additionally, the study took place in the PACU which is considered a noisy location due to the high fluctuation of patients.

Our study has several limitations that should be addressed. So, the number of included patients was relatively low. Expectedly, only a few patients suffered from severe pain because of the intraoperative pain management. But, even moderate NRS scores are clinically relevant and must be treated adequately.

Conclusion

In conclusion, patient-associated factors, environment-related factors and the type of surgery influence the autonomic nervous system and consecutively also the ANI. Therefore, objective monitoring of pain remains a big challenge - especially in awake, postoperative patients. In conclusion, ANI did not improve

postoperative pain management in this study. Interestingly, some patients showed a paradox correlation between NRS and ANI. Further studies must be undertaken to evaluate the reason of different correlations.

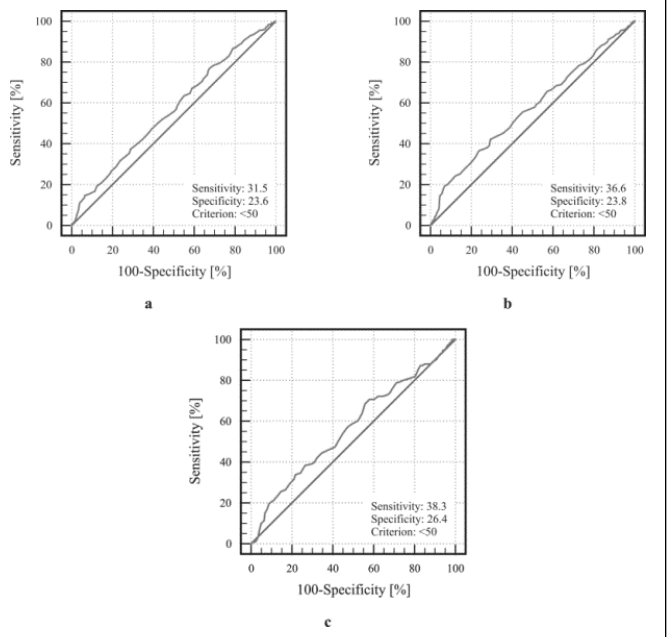

Figure 3: ROC analysis for pain detection using an ANI threshold of <50. (a) For detection of NRS>2, sensitivity and specificity were 31.5% and 76.4%. (b) For detection of NRS>4, sensitivity and specificity were 36.6% and 76.2%. (c) For detection of NRS>6, sensitivity and specificity were 38.3% and 73.6%.

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Prior Presentation

Interim data from this work were presented at the Congress of the Scandinavian Society of Anesthesiology and Intensive Care, June, 10th 2015, in Reykjavik, Iceland.

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