Official title: Treatment of acute exacerbations of chronic obstructive pulmonary disease with acupuncture during hospitalization: a three-arm double-blinded randomized sham-controlled trial

NCT number: NCT03398213

Date of the document: June 3, 2020

Methods:

Study design: This is a three-arm 1:1:1 randomized-controlled trial evaluating the efficacy and safety of the addition of acupuncture to SOC as compared to sham-procedure added to SOC (sham-control) and to SOC only (SOC-control) for treatment of AECOPD in patients hospitalized in internal medicine departments. The study protocol was reviewed and approved by the Institutional Review Board (IRB) in accordance with the Helsinki Declaration (0108-17-BNZ) and registered at www.clinicaltrials.gov (NCT03398213). Trial methods and results were reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[19]

Participants: Patients hospitalized in internal medicine departments with a previous diagnosis of COPD[3] were evaluated by department physicians. Inclusion criteria included a previous diagnosis of COPD and a clinical diagnosis of AECOPD as defined by the GOLD criteria.[3] Exclusion criteria included hemodynamic instability, a platelet count below $20x10^9$/L, expected respiratory deterioration requiring mechanical ventilation in the next 24 hours, or an inability to provide informed consent. Primary socio-demographic and medical data were recorded and compared between the three study groups.

Setting: The study was set in internal medicine departments of Bnai Zion medical center, a tertiary hospital in Haifa, Israel.

Interventions: The intervention protocol was based on a literature review and the Delphi process. A panel of eight acupuncturists of at least 5 years of experience in treating hospitalized patients were consulted. The experts were asked to review and analyze the literature regarding Traditional Chinese Medicine (TCM) and COPD, delineate relevant TCM syndromes and associated "critical" acupoints and treatment frequency. Their suggestions were based on literature data and their professional experience. Finally, three cycles of stepwise anonymous discussions were taken to obtain a consensus on the treatment approach. The conclusion was to

assign the patients into three groups for four daily consecutive treatment sessions and a 4-day follow-up.

Standard-of-care (SOC) only: Patients received SOC for AECOPD according to a standard protocol based on the GOLD guidelines.[3] Such therapy included oxygen to maintain saturation around 90%, inhalations, antibiotics and systemic corticosteroids for five days. Noninvasive or mechanical ventilation were added depending on the severity of the AECOPD, as determined by clinical evaluation and blood gases.

True acupuncture + SOC group: Acupuncture treatment was documented according to STRICTA guidelines.[20]

- Acupuncture rationale: The acupuncture was performed in a TCM style. During the Delphi process, a list of acupoints relevant to acute lung conditions were determined and associated with different TCM syndromes. Practitioners systematically documented syndrome diagnosis according to TCM reasoning and used only acupoints appearing in the list and corresponding to the TCM diagnosis.
- Details of needling: During the treatment, the acupuncturists used 75% alcohol pads to sterilize the skin around the acupoints. Subsequently, sterile disposable needles were inserted in the acupoints. An average of five Eco FDA-approved needles of 3-cm length and 0.22-mm diameter were inserted. The puncture depth varied with anatomical location from 0.5 to1 cm. Manual needle stimulation was performed, but *de qi* sensation (e. g. dullness, sourness, heaviness, tingling sensation around the needle) was not sought.
- Treatment regimen: Four daily consecutive 15-20-minute sessions were administered.
- Other components of treatment: Patients in this group also received SOC as described earlier. No other complementary medicine therapies were added. Explanations were given to patients on potential benefits and side effects of acupuncture and treatment was administered only after they signed informed consent.
- Practitioner background: The treatment was administered by eight acupuncturists with at least 5 years of clinical experience in a hospital setting.
- Control intervention: The two control groups were SOC only (SOC-control) and SOC with sham-procedure (sham-control).

Sham-procedure + SOC group: Department physicians underwent a one-hour training on placing plasters on ear-points that have no relevance to lung conditions. During this training,

they were taught they are actually treating patients by stimulating ear acupoints and that the aim of the study was to compare the efficacy and safety of acupuncture administered by an experienced acupuncturist as compared to acupressure administered by unexperienced medical staff after a short training. Patients were told they are receiving ear-point stimulation. Therefore, this study arm was double blinded. SOC was administered as well as described earlier.

Outcomes:

The primary outcome was dyspnea intensity pre- and post-treatment in the 4 days of follow-up. It was measured daily, before and one hour after treatment (for acupuncture and sham-control groups) or after first evaluation (for SOC-control group), via the modified Borg (mBorg) scale, which is a validated scale that has been used to evaluate the degree of dyspnea (0- no dyspnea, to 10- worse dyspnea) in both stable COPD and AECOPD.[21,22] Dyspnea intensity was chosen as primary outcome since it has been shown to predict clinical outcomes in AECOPD.[23]

Secondary outcomes included:

Variation of clinical symptoms: Including cough intensity and sputum production associated with the AECOPD, as evaluated on a Visual Assessment Scale from 0 (no symptom) to 10 (maximally symptomatic), throughout the 4 days of evaluation.

Variation of physiologic features: Venous blood gases (pH and pCO_2) and oxygen saturation were measured before intervention and daily in the four evaluation days. Respiratory rate (RR) was measured daily, before and one hour after treatment (for true acupuncture and sham-control groups) or after first evaluation (for SOC-control group).

Treatment failure: Defined as death during hospitalization or need for noninvasive or mechanical ventilation. Treatment failure incidence was evaluated and compared between the three groups.

Duration of hospitalization: Evaluated and compared between the three study arms.

Safety: Acupuncture-related side effects were systematically evaluated after treatment in the true acupuncture group via the validated Acup-AE questionnaire administered to the patient by the acupuncturist immediately after therapy.[24]

Minimal sample size: In a previous study evaluating the efficacy of acupuncture vs sham-acupuncture in 68 patients with chronic COPD (34 patients in each group), a 3.6±1.9 units improvement in dyspnea (according to mBorg scale) was found in the acupuncture arm, as

compared with a 0.4±1.2 units improvement in the sham-acupuncture arm.[8] According to these data and ANOVA test with alpha of 0.05 and an 80% power, we calculated a minimal sample size of 66 patients (22 in each group) for the current study.

Randomization: Patients meeting inclusion/exclusion criteria were randomized to either SOC with acupuncture (true acupuncture), SOC with sham-procedure (sham-control) or SOC only (SOC-control) using 1:1:1 permuted block randomization. The permuted block randomization list was generated by Excel software. To guarantee allocation concealment, randomization was done by an independent research assistant who did not participate in any other parts of the research and assigned the group code to each participant according to the randomization list. The independent research assistant was blinded to the meaning of the group code.

Blinding: Data collectors, department physicians, physicians administering the sham-procedure and the statistician were blinded to the group allocation status; acupuncturist blinding is clearly not possible, however, contact time with patients was the same in both true acupuncture and sham-control arms (15-20 min). Patients receiving both true acupuncture and sham-procedure were told they are treated for their respiratory condition by acupuncture/acupressure. The group allocation status was revealed after completion of the study.

Statistical analysis: Demographic and clinical data was analyzed at baseline to measure the balance among the study groups. Quantitative variables were described using mean ± standard deviation or median and 25^{th}-75^{th} percentiles (Q1, Q3) depending on their distribution. Qualitative variables were described using frequency and percentage distributions. Next, we showed that our variables distribute equally between the study groups. For comparing normally distributed variables between our study groups, we used the ANOVA test. For comparing variables that do not distribute normally between our study groups, we used the Kruskal-Wallis test with adaptation to pairwise comparison. For comparing qualitative variables between our study groups, we used the independent Chi-square test and Fisher exact test. Bonferroni adjustment was used for multiple comparisons for each independent comparison of true acupuncture vs sham-control, true acupuncture vs SOC-control and sham-control vs SOC-control. Since the variation of dyspnea intensity between day 1 and day 2 had a normal distribution, a multivariate linear regression analysis was performed after collinearity, interaction and confounding analysis, in order to neutralize the effect of the different sociodemographic and medical covariates on the primary outcome in the 3 study arms. The adjusted unstandardized regression coefficients were given with confidence interval (CI), while

a $p<0.05$ was considered as statistically significant. Data analysis was performed using IBM SPSS version 22 statistics software.

Results:

Baseline patient data: 104 patients were screened for eligibility from November 2017 to February 2020. Among them, 72 met inclusion criteria and were recruited. Twenty-six of them were assigned to the true acupuncture arm, 24 to the sham-control arm, and 22 to the SOC-control arm. Baseline demographic and clinical characteristics were similar in patients from the 3 study arms as shown in Table 1. To note, all the patients randomized to any of the three groups completed treatments per-protocol (Fig. 1).

Primary outcome: Baseline dyspnea was similar in the three groups. A statistically significant difference between the three groups in dyspnea intensity was found from the first day of evaluation after treatment (median [Q1, Q3] mBorg score 5.0 [4.0, 5.0] in true acupuncture, 6.0 [4.25, 7.875] in sham-control and 7.5 [5.5, 8.0] in SOC-control, p=0.014 – significant difference of both true acupuncture vs sham-control: p=0.031, and true acupuncture vs SOC-control: p=0.014, but non-significant between sham-control and SOC-control: p=0.34), and until day 3 after treatment (Fig. 2A). After adjustment for such covariates in a multivariate linear regression analysis, the association of study arm with improvement of dyspnea from day 1 to day 2 remained statistically significant (Table 2).

Secondary outcomes:

- *Patient-reported outcomes*:

Baseline VAS scores for cough and sputum intensity were similar in the three study arms (Table 1). No statistically significant difference in the cough intensity was observed between the three study arms throughout the 4 days of follow-up (Fig. 2). However, a statistically lower level of sputum production was observed in the true acupuncture arm as compared with sham-control and SOC-control from day 2 (p=0.04) (Fig. 2). Post-hoc analysis showed a statistically significant difference between true acupuncture and sham-control in day 2 (p=0.024), day 3 (p=0.010) and day 4 (p=0.018), while only on day 2 between true acupuncture and SOC-control (p=0.044), and no statistically significance between sham-control and SOC-control.

- *Physiologic assessment*:

Baseline physiologic data were similar in the three groups (Table 1). A statistically significant difference was observed in respiratory rate (RR) at day 2 after treatment (p=0.002), with significant difference both between true acupuncture and sham-control (p=0.005) and between true acupuncture and SOC-control (p=0.003), but not between sham-control and SOC-control

(p=0.050), while all other RR measurements were statistically similar between the 3 arms throughout the 4-day follow-up (Fig. 3A).

Concerning pH, a statistically significant difference was observed at day 4 between the 3 groups (p=0.048), although post-hoc analysis did not show any statistical significance when comparing groups head-to-head (Fig. 3C).

No statistically significant difference was observed when comparing other physiologic measures between the 3 study groups (Fig. 3).

- *Treatment failure*:

No death or mechanical ventilation occurred in the study participants during follow-up. However there had a total of 4 treatment failures, all of them were non-invasive ventilations, which occurred in 2 (8%) patients in the true acupuncture arm, 1 (4.3%) in the sham-control arm and 1 (5%) in the SOC-control arm (p=0.83).

- *Duration of hospitalization*:

No difference was noted in terms of duration of hospitalization between the three study arms (5.5±2.3 days for true acupuncture vs. 6.0±2.9 days for sham-control and 6.3±2.9 days for SOC-control, p=0.050).

- *Safety*:

No side effect of acupuncture treatment was reported during the study period as assessed by the Acup-AE questionnaire.

Tables and Figures:

Table 1: Baseline characteristics

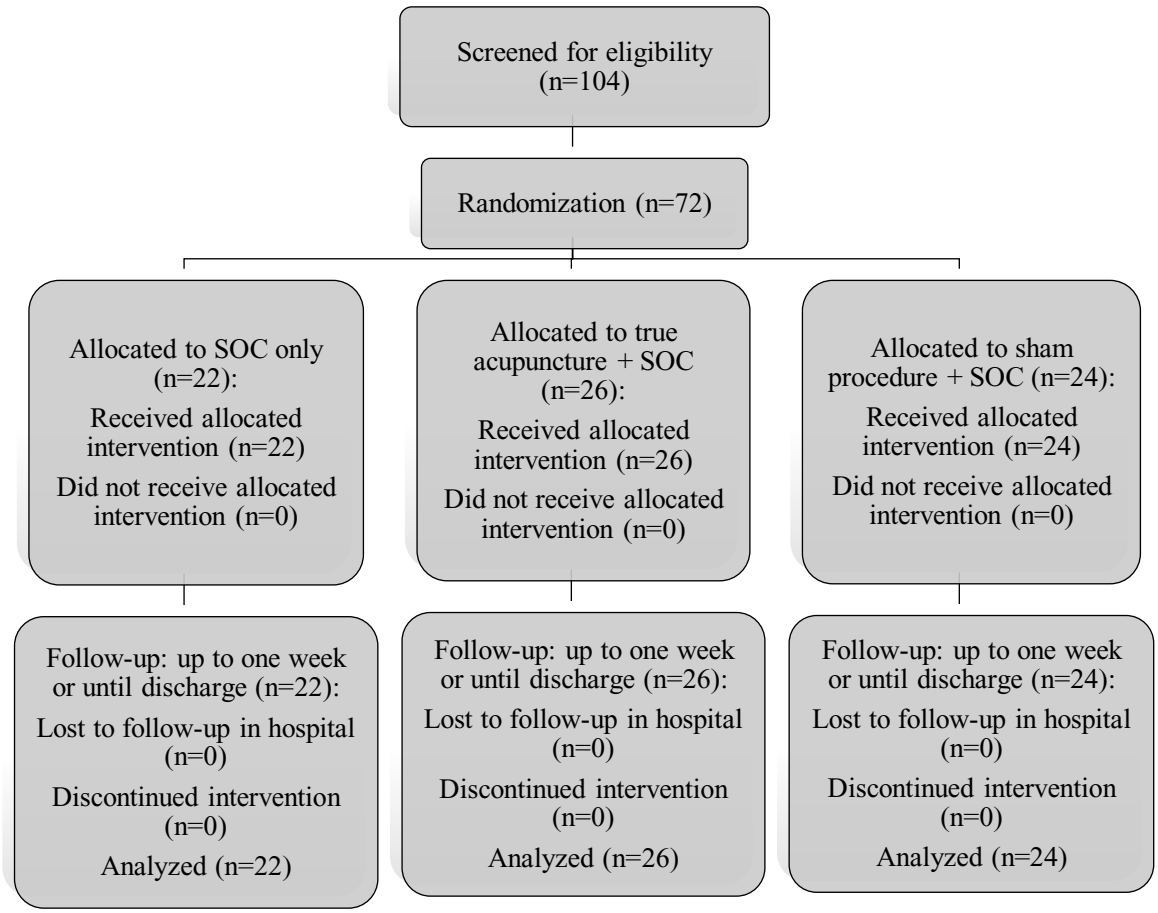
Characteristics	**True acupuncture (N=26)**	**Sham-control (N=24)**	**SOC-control (N=22)**	**p**
Age (mean ± SD)	69.2±10.1	70.7±8.1	67.4±9.3	0.47
Gender (Men)	20 (77%)	15 (62%)	17 (77%)	0.43
Comorbidities				
Cardiovascular	18 (69%)	20 (83%)	15 (68%)	0.42
Respiratory (other than COPD)	7 (27%)	2 (8%)	5 (23%)	0.23
Gastroenterological	2 (8%)	4 (17%)	5 (23%)	0.34
Renal / Urologic	7 (27%)	3 (12%)	5 (23%)	0.44
Metabolic / Endocrinological	15 (58%)	13 (54%)	13 (59%)	0.94
Hematological / Oncological	3 (12%)	6 (25%)	3 (14%)	0.40
Neurological	4 (15%)	0 (0%)	1 (5%)	0.09
Smoking status				
Smoker	13 (50%)	16 (67%)	14 (64%)	0.44
Former smoker	13 (50%)	8 (33%)	8 (36%)	
Never smoked	0	0	0	
CCI (median [Q1, Q3])	6.0 [3.5, 6.0]	5.0 [4.0, 6.75]	4.5 [3.0, 7.25]	0.87
COPD severity				
Mild: FEV1 ≥ 80%	1 (4%)	0 (0%)	1 (5%)	
Moderate: 50% ≤ FEV1 < 80%	4 (15%)	5 (21%)	5 (23%)	0.69
Severe: 30% ≤ FEV1 < 50%	7 (27%)	11 (46%)	9 (41%)	
Very severe: FEV1 < 30%	5 (19%)	4 (17%)	4 (18%)	
Unknown	9 (35%)	4 (17%)	3 (14%)	
Pulmonary hypertension				
None	10 (38%)	15 (62%)	16 (73%)	
Mild: mPAP = 25-40 mmHg	4 (15%)	3 (12%)	3 (14%)	
Moderate: mPAP = 41-55 mmHg	3 (12%)	0	2 (9%)	0.11
Severe: mPAP > 55 mmHg	0	0	0	
Unknown	9 (35%)	6 (25%)	1 (5%)	
COPD exacerbation hospitalizations				
0	19 (73%)	12 (50%)	9 (41%)	
1-4	6 (23%)	11 (46%)	9 (41%)	0.09
≥5	1 (4%)	1 (4%)	4 (18%)	
Treatment				
Inhalations	24 (92%)	23 (96%)	22 (100%)	0.41
Systemic corticosteroids	3 (12%)	3 (13%)	1 (5%)	0.61
Theophylline	0	0	1 (5%)	0.32
Oxygen home therapy	8 (31%)	12 (52%)	8 (36%)	0.29
BiPAP	4 (15%)	2 (8%)	4 (18%)	0.60
APACHE-II at admission (mean ± SD)	13.3±3.6	12.0±4.4	11.0±3.8	0.14
Baseline data (median [Q1, Q3])				
Dyspnea (mBorg)	8.0 [5.5, 8.75]	6.5 [5.0, 8.5]	7.75 [6.0, 8.5]	0.82
Cough (VAS)	7.5 [5.0, 8.0]	5.0 [5.0, 7.4]	5.0 [3.6, 7.5]	0.35
Sputum (VAS)	6.0 [1.5, 7.5]	6.0 [4.25, 6.0]	5.0 [1.9, 6.0]	0.22
O_2 saturation				
≤ 80%	4 (15%)	1 (4%)	0	0.30
81-89%	9 (35%)	10 (42%)	10 (45%)	
≥ 90%	13 (50%)	13 (54%)	12 (55%)	
PCO_2 (mmHg)				
< 45	6 (23%)	3 (12%)	8 (36%)	
45-60	12 (46%)	17 (71%)	9 (41%)	0.10
60-80	5 (19%)	4 (17%)	5 (23%)	
> 80	3 (12%)	0	0	
pH				
< 7.2	0	0	0	
7.2-7.3	5 (19%)	4 (17%)	1 (5%)	0.30
> 7.3	21 (81%)	20 (83%)	21 (95%)	
Respiratory rate (/min) (median [Q1, Q3])	21 [16, 23.75]	22 [16.5, 26]	20 [16, 22]	0.26

Legend: CCI: Charlson Comorbidity Index; mPAP: Mean Pulmonary Arterial Pressure; SOC: Standard-Of-Care.

Table 2: Multivariate linear regression analysis on variation of dyspnea from day 1 to day 2

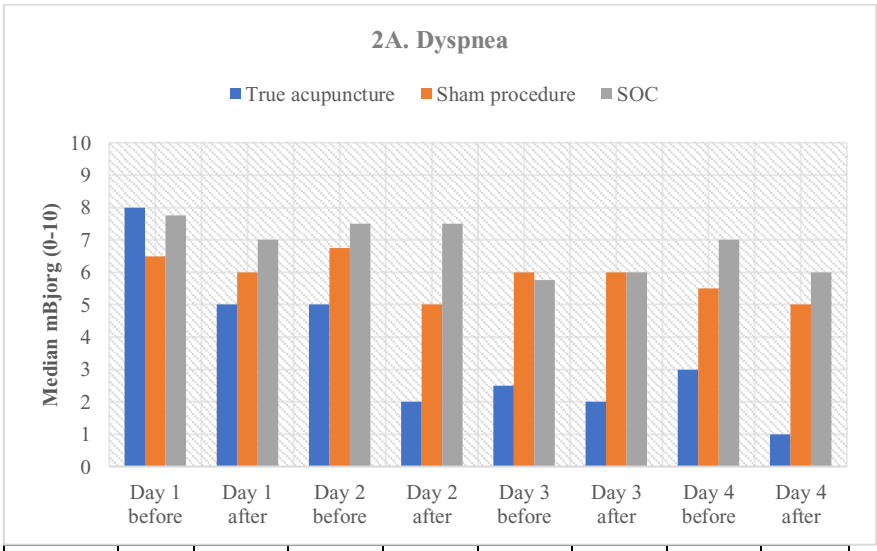
Factors and covariates	Adjusted unstandardized coefficient (B)	95% Confidence interval		p value
		Inferior	Superior	
Constant (Intercept)	2.088	-3.409	7.584	0.457
Study Arm				
True acupuncture	2.172	0.421	3.923	0.015
Sham-control	0.390	-1.319	2.099	0.655
SOC-control	0	-	-	-
Cardiovascular comorbidities (0=No, 1=Yes)	-0.322	-2.935	1.391	0.713
Gastroenterological comorbidities (0=No, 1=Yes)	4.703	2.527	6.879	<0.001
Hospitalizations for COPD in the last year	-0.379	-0.756	-0.003	0.048
Age	-0.040	-0.133	0.053	0.400
APACHE-II	0.118	-0.099	0.336	0.287
Charlson Comorbidity Index	-0.026	-0.406	0.354	0.894

Figure 1: Flow-chart

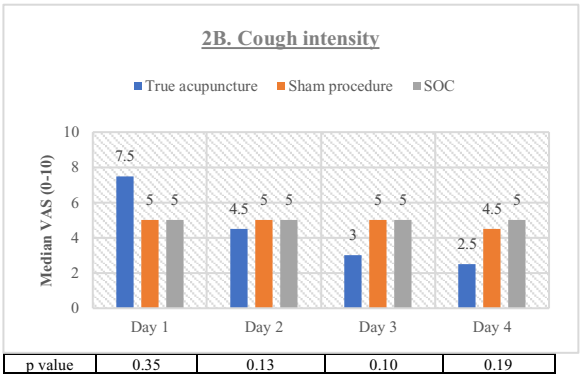


Legend: SOC: Standard-of-care.

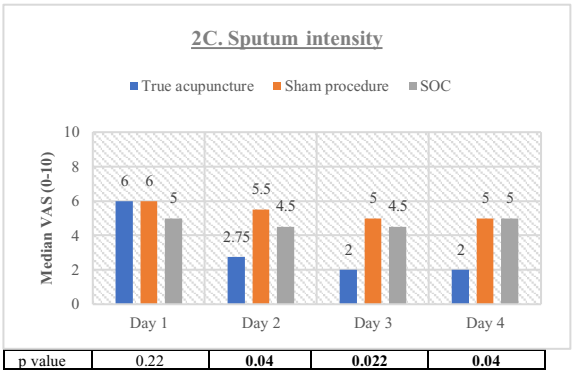
Figure 2: Between-group comparison of patient-reported outcomes



p value	0.82	**0.014**	**0.019**	**0.002**	**0.003**	**0.009**	0.053	0.067

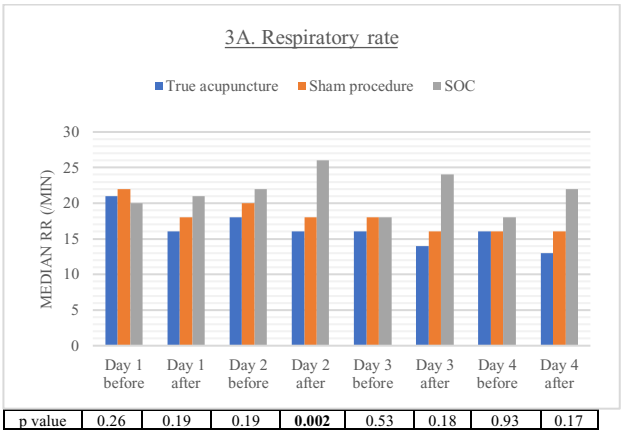


p value	0.35	0.13	0.10	0.19

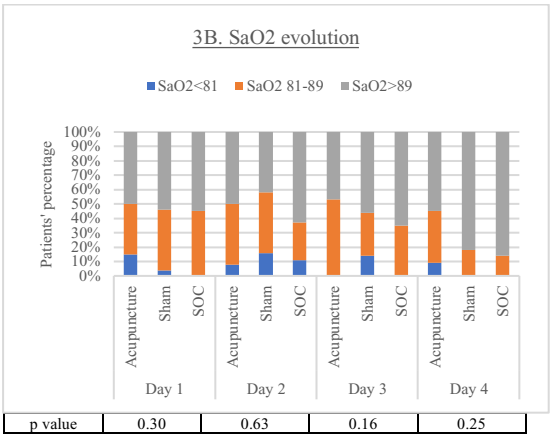


p value	0.22	**0.04**	**0.022**	**0.04**

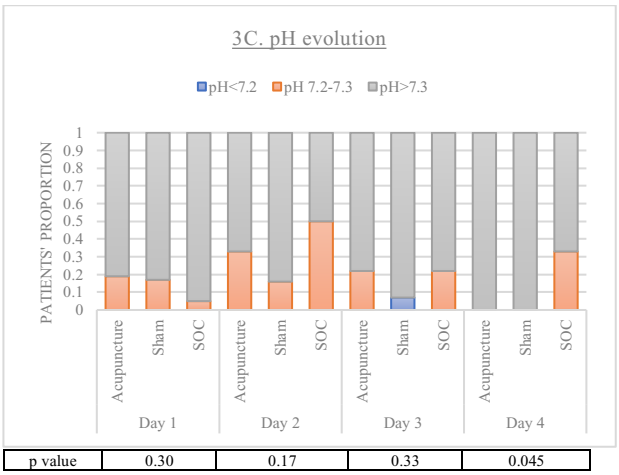
Figure 3: Between-group comparison of physiologic features



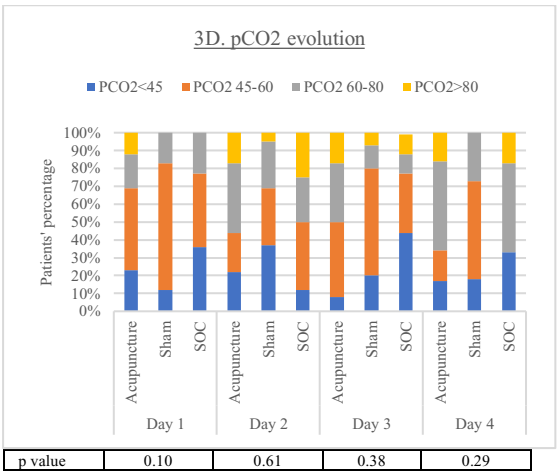
p value	0.26	0.19	0.19	**0.002**	0.53	0.18	0.93	0.17



p value	0.30	0.63	0.16	0.25



p value	0.30	0.17	0.33	0.045



p value	0.10	0.61	0.38	0.29