Effect of Rectal Midazolam on Pain, Stress, and Cooperation of Patient during Urodynamic Test in Women: A Randomized Clinical Trial

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Key Words: cooperation; midazolam; pain; sedation; stress; urodynamic; women

Abstract:

Purpose: The urodynamic study is an invasive test, and causes pain and stress in the patient. We have investigated the effect of rectal midazolam sedation on the pain, stress, and cooperation of women performing urodynamic study.

Materials and Methods: At the present randomized clinical trial (RCT) from January to July of 2021 a total of 84 women were prospectively randomized to undergo urodynamic study with or without sedation. The primary outcome of interest was experienced pain during urodynamic study. In the intervention group, after monitoring baseline vital signs (heart rate, blood pressure, O_2 saturation), sedation was done with rectal midazolam at a dose of 0.3 mg/kg (maximum 15 mg). Completing the procedure, after recovery from sedation patients were asked to fill a self-assessed visual analog pain scale (VAS, 0-10), 5-point visual stress scale (1-5) and, patient collaboration level during urodynamic study was evaluated by nurse with a researcher-made tool (0-3). In the control group test was performed in routine practice with no sedation. Baseline vital signs measured pre and intra-procedural time, as well as their experienced pain, stress, and cooperation levels were recorded.

Results: 84 female cases were evaluated. In terms of comparison of changes in pre and intra-test physiologic parameters, results showed that there were no significant differences between the two groups for all physiologic parameters: SBP, DBP, PR, SpO_2. Analysis of the pain score showed that it was lower in the intervention group, and there was a significant difference in pain score between the two groups (***P* =.024**). While the stress and corporation scores were not reported statistically significant (*P*=.388 and *P*=.955, respectively).

Conclusion: Sedation with rectal midazolam in adult women before UDS is safe and effective in reducing pain but is not effective in reducing stress and increasing cooperation. The amount of pain based on the visual analog pain scale is mild and although this method is safe, its use routinely is not recommended.

Introduction:

The urodynamic study (UDS) is an invasive test that allows the assessment of lower urinary tract symptoms in women. Urethral and rectal catheterization is necessary for this test. The patient must urinate in the presence of a technologist in an unknown environment. These may lead to pain and stress and affect the test results and patient cooperation.[1-4] Various methods have been implemented in previous studies to solve this problem, such as the use of educational pamphlets, a head pad, and videos or the playback of music or inhalation of vegetable oils

during testing.[5-10] Sedation with midazolam before UDS is another method used in various studies for children, and has been effective at calming the child and performing the test better without affecting the test results.[11-15]

Midazolam is a benzodiazepine with sedative and anti-anxiety effects which provides partial ante-grade amnesia. With a rapid-onset and short-effect, it can be administered through various ways such as oral, nasal, intravenous, and rectal. It has no serious side effects.[12,13]

No studies have assessed the effect of sedation on adult females undergoing UDS. We have investigated the effect of rectal midazolam sedation on the pain, stress, and cooperation of women performing UDS.

PATIENTS AND METHODS

Study population

In the present study participants were women who were diagnosed with lower urinary tract symptoms (LUTS) from January to July of 2021. Patients were enrolled in the study after a routine pre-procedural evaluation. Inclusion Criteria were the women between the age of 20-80 years old who were referred to our urodynamic center for evaluation of lower urinary tract symptoms.

Exclusion criteria were active urinary tract infection, history of cardiovascular and respiratory disease, known psychiatric diseases, neurologic disorders, spinal cord injury, any analgesic use in the last 24 hours, and anxiolytic or sedative drug use 10 days before the test. By researchers study objectives were explained to each of the participants and informed consent was obtained.

Ethics committee approval was obtained from Isfahan University Of Medical Sciences. Ethical code was ××× and IRCT code was ×××. Patients' enrollment algorithm has been illustrated in **Figure 1**.

Study design

This study was a prospective single center, parallel-group randomized clinical trial with balanced randomization [1:1] which was performed in outpatient urodynamic clinic of Khorshid hospital in Isfahan, Iran. Sample size was calculated considering 0.62 t expected difference between with and without sedation groups in the primary outcome of interest.

Considering type I error of 0.05 and type II error of 0.2 based on $n = \left[\frac{2(z_{1-\alpha/2}+z_{1-\beta})^2}{\Delta^2} + \frac{z_{1-\alpha/2}^2}{4}\right]$[4], 42 samples were estimated in each group. Therefore, 84 samples were needed totally.

Patients were randomly assigned to one of the two groups of with and without sedation (42 patients in each group). Randomization was done using computerized random numbers. The allocated procedure for each patient was recorded in concealed envelopes. Considering inclusion/exclusion criteria and after achieving patient's agreement on participation, the concealed envelopes were opened by one of the researchers and the allocated procedure was performed as explained below.

Procedure technique

All procedures in both groups were performed by standardized UDS (uroflowmetry and pressure-flow study) along with EMG (Electromyelography) according to the International Continence Society recommendations. All cases were conducted in an outpatient urodynamic clinic managed by a female Urologist with the assistance of an experienced and special urodynamic nurse.

In the intervention group (with sedation), before the procedure after monitoring baseline vital signs (heart rate, blood pressure, O_2 saturation), sedation was done at a dose of 0.3 mg/kg (maximum 15 mg) of midazolam. Midazolam was administered rectally using an 8 Fr feeding tube by the urodynamic nurse. Fifteen minutes later the vital signs were re-evaluated, the next uroflowmetry was done, and the post-void residue was measured, then pre-lubricated gel urethral(7 Fr) and rectal catheters(9 Fr) were introduced, and three electrodes were attached to the perineum to record EMGs by a single urodynamic nurse in a dorsolithotomy position. After installing the catheters a pressure-flow study was performed using the standard method according to ICS recommendations.[16] The electrodes and catheters were finally removed at the end of the procedure. In the control group (without sedation) all steps of test were performed in routine practice with no sedation. Baseline vital signs measured pre and intra-procedural time in both groups.

Outcome assessment

The primary outcome of interest was pain during UDS, so after completing the procedure, when recovery from sedation was achieved patients in the intervention group were asked to fill a self-

assessed visual analog pain scale (VAS, 0-10), but In the intervention group immediately after the procedure, level of pain was evaluated and recorded.

As secondary outcomes, patient's stress and collaboration during UDS were respectively evaluated with a 5-point visual stress scale (1-5) and a researcher-made collaboration level tool (0-3).

Statistical analysis

Quantitative variables were expressed as mean ± SD and qualitative variables were expressed as counts (percent). Independent t-test was used to compare mean of quantitative variables between groups. Chi-square test was applied to compare the distribution of categorical variables across study groups. Exact test was used if the main assumption underlying Chi-square test, no expected cell counts less than 1 and at most 20% of expected cell counts less than 5, was not met. The differences of peri and intra-procedural physiologic parameters in each group were assessed by non-parametric Wilcoxon Signed Ranks Test. We applied analysis of covariance (ANCOVA) to compare mean changes in pre and intra-test physiologic parameters between two groups. Mann-Whitney non-parametric test based on peri and intra-procedural differences was alternative one when the assumptions of ANCOVA or Student t-test were not met. The assumptions underlying Independent t-test including normality and homogeneity of variance were assessed by Shapiro-Wilk and Levene's tests, respectively. The main assumptions underlying ANCOVA including homogeneity of variance and no interaction between group (groups of study) and covariate (pre measurement) variables were also evaluated by Levene's test and including interaction terms in regression model, respectively. All analyses were performed using IBM SPSS Statistics 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows,Version 25.0. Armonk, NY: IBM Corp). *P* value < .05 was considered statistically significant.

Results:

From January to July 2021, 352 women were referred to our urodynamic center, of which 84 females aged 20-65 years were included in the study. The rest either did not meet the inclusion criteria or did not agree to participate in the study **Figure 1**. The mean age of the 42 patients in intervention group was 46.55 ± 12.64 years and 42 patients in control group was 55.48 ± 17.05 years and there was significant difference in age between two groups [mean

difference, 95%CI: -8.93, (-15.50,-2.35); P =.008]. The mean weight of patients in intervention and control groups was 73.10 ± 12.32 and 74.93 ± 14.26 kg, respectively. No significant difference was found in weight distribution between two groups [mean difference, 95%CI: -1.83, -7.68, 4.02); P =.535] **Table 1**.

Regarding the differences of peri-procedural physiologic parameters in each group, in sedated group SBP [mean difference, 95%CI: -3.09, -6.05,-0.14); P =.045], DBP [mean difference, 95%CI: -1.67, -3.19,-0.14); P =.035], and SpO_2 [mean difference, 95%CI: -0.48, -0.84,-0.11); P =.021] were statistically significant, but in non-sedated group only PR was significant [mean difference, 95%CI: -2.70, -4.79,-0.61); P =.026] **Table 2 Figure 2**.

In terms of comparison of changes in pre and intra-test physiologic parameters, results showed that there were no significant differences between the two groups for all physiologic parameters: SBP (P-value=.416), DBP (P-value=.520), PR(P-value=.075), SpO_2 (P-value=.066) **Table 3**.

Analysis of the pain score showed that it was lower in intervention group, and there was significant difference in pain score between two groups (*P*=.024). While the stress and corporation scores were not reported statistically significant (*P*=.388 and *P*=.955, respectively) **Figure 3**.

Further analysis showed that there are no significant differences in mean age among pain intensity and stress level (*P*=.481, *P*=.667, respectively).

Comparison of pain intensity between the two groups based on the three ranks including severe, moderate, and mild showed that there is no significant relationship between pain intensity and study groups **Table 4**.

Discussion:

In this study (RCT), we investigated the effect of sedation with rectal midazolam on pain, stress, and cooperation of adult women during an UDS. According to the results, the effects of rectal midazolam in reducing pain were significant but did not affect patients' stress and cooperation. In this study, the rectal midazolam sedation in women was safe. Fluctuations in vital signs and O_2 saturation were not significant before and after midazolam administration, compared to the control group. The mean score of pain and stress based on the visual analog scale in both groups were reported to be in the mild range and shows that UDS is well-tolerated in adult women with or without sedation.

Previous studies examining patients' pain and stress during UDS have reported similar results in terms of pain and stress.[1,4,17] In Xavier Biardeau's study, about 60% of people experienced pain. Pain score was higher in men and younger people.[2] In another study, women's attitudes toward UDS have been specifically examined and according to their results 42% of women experienced stress during the test and 27% reported moderate to severe pain. The pain was less at older ages and women who were referred from specialized urogynecology centers.[17] In another study conducted specifically on women, the mean pain rate based on a visual analog scale was 1.5 out of 10, which was slightly lower than our results, and the mean stress was 1.8 out of 10. The pain was more common in women with overactive bladder and painful bladder syndrome and younger women with a history of depression.[4]

Numerous studies have examined the effects of different items to reduce pain and stress during the UDS. Two studies have examined the result of listening to music, None of them has not been effective in reducing pain and stress.[5,7] In one of these studies, the use of educational pamphlets was also examined simultaneously, which also have no significant effect on reducing pain and stress.[5] Another study examined the effect of inhaling vegetable oils such as Salvia sclarea or Lavandula angustifolia on reducing stress in patients during an UDS. According to the results of this study, inhaling Lavandula oil reduces stress in women, and inhaling Salvia sclarea oil calmed down.[9]

In animal studies, the effect of midazolam on UDS results has been investigated. Studies in female cats have shown that alertness has no effect on urodynamic variables in cats and sedation with midazolam reduces animal stress during testing.[18,19]

The effects of midazolam administration in different routes (oral, nasal, and rectal) have been studied in several studies in children to reduce stress and perform UDS and other painful interventions better and easier.[11-13,20] Contrary to the theory that benzodiazepines can relax the pelvic floor muscles and alter UDS results,. in these studies it was seen that the use of midazolam in children did not change the test results and due to the sedative and anti-stress effects of midazolam, the test was performed more easily in children. Also, in all these studies, the use of midazolam to any of the ways has been safe and effective, as well as effective in calming children and performing the test better.[11-13]

To date, no study has examined the effect of rectal midazolam in adult women UDS before.

According to the results of our study rectal midazolam has been effective in reducing patients' pain during the test and this method can be used in patients who experience more pain and do not cooperate properly due to pain or in women with underlying conditions and diseases which raises the possibility of more pain tolerance such as painful bladder syndrome. Because the pain intensity during the test is in the mild range in our and the similar studies, apply of this sedation method for all women to reduce pain in the UDS does not seem appropriate.

In our study, due to ethical considerations, the test was performed once in patients and it was not possible to evaluate the effects of midazolam on test results and it was the limitation of our study.

Conclusion:

According to the results of our study, the use of rectal midazolam in adult women before UDS is safe and effective in reducing pain, but is not effective in reducing stress and increasing cooperation. The amount of pain based on visual analog pain scale is mild and although this method is safe, its use routinely is not recommended.

Acknowledgments: We would also like to thank urodynamic clinic staff of Khorshid Hospital in Isfahan, Iran who cooperated in the implementation of this study.

Conflicts of interest:

None of the authors of this study, individuals or devices have a conflict of interest in writing or publishing this article.

Data availability:

The data used to support the findings of this study are included within the article.

Funding:

Nil.

Patient consent:

The authors certify that they have obtained all appropriate patient consent forms. All patients have signed an informed written consent for demographics and other clinical information to be

reported in the journal. The patients understood that their name and initials will not be published and due efforts will be made to conceal identity.

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Clinical trial registration:

IRCT code of this study (IRCT20210122050105N1) was received on 25/01/2021.

Ethics of approval:

This study was registered as a research project in the Vice Chancellor for Research of the Faculty of Medicine in Isfahan University Of Medical Sciences and on 03/01/2021 from the Ethics Committee in Biomedical Research Ethics Code with reference number IR.MUI.MED. Received REC.1399.881. The subject has obtained the patients' informed written consent to publish their information and details.

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Table 1. Demographic characteristics of each groups.

Variable	Sedated Group (N = 42)	Non-sedated Group (N = 42)	*P*-value
Age, year; mean ± SD	46.55 ± 12.64	55.48 ± 17.05	.008
Weight, kg; mean ± SD	73.10 ± 12.32	74.93 ± 14.26	.535

P-value obtained based on Independent t-test.

Table 2. Comparison of peri-procedural physiologic parameters in each group.

Variable	Sedated Group (N = 42)	*P*-value	Non-sedated Group (N = 42)	*P*-value

	pre-test	intra-test		pre-test	intra-test	
SBP, mmHg; mean ± SD	112.86± 16.273	109.7± 13.523	.045	118.25±17.670	115±15.359	.097
DBP, mmHg; mean ± SD	75.48±10.866	73.81±11.033	.035	79.75±10.975	78.75±8.825	.384
PR, b.p.m; mean ± SD	82.24±12.579	82.02±10.706	.690	81.65±16.041	78.95±14.131	.026
SpO_2, %; mean ± SD	95.38±2.141	94.90±2.229	.021	94.60±2.898	94.75±2.239	.856

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, Pulse Rate; SpO_2 , Blood Oxygen Saturation. **P-value obtained based on Wilcoxon Signed Ranks Test.**

Table 3. Comparison of peri-procedural physiologic parameters between two groups

Variable	***P*-value**
SBP, mmHg;	.416[a]
DBP, mmHg;	.520[b]
PR, b.p.m;	.075[a]
SpO_2, %;	.066[b]

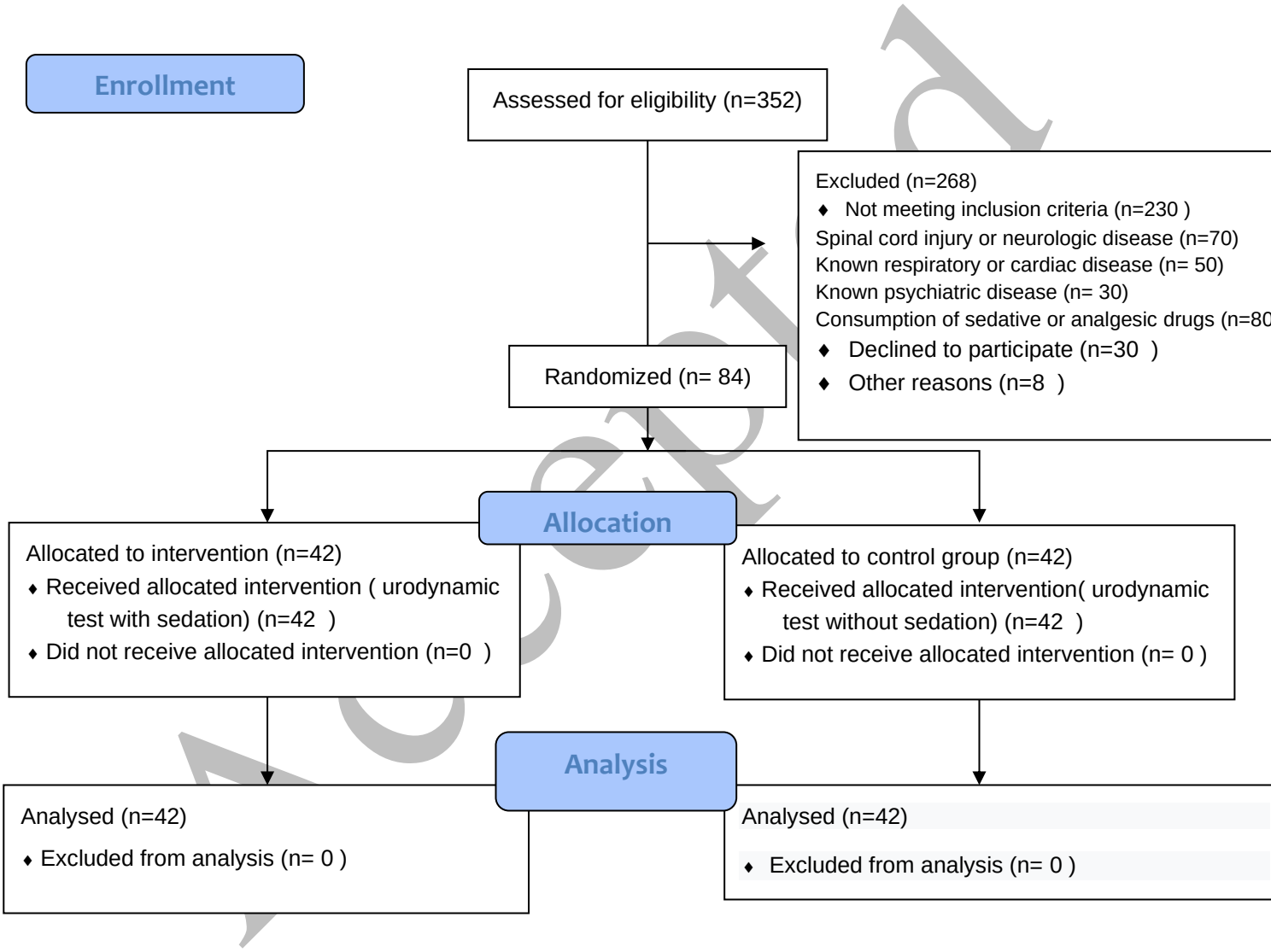
[a] **P-value obtained based on ANCOVA**

[b] **P-value obtained based on Mann-Whitney Test for peri and intra-procedural differences**.

Table 4. Comparison of Intra-test pain intensity between the two groups
P-value obtained based on Exact test.

Variable	**Intensity**	**Sedated Group (N = 42)**	**Non-sedated Group (N = 42)**	***P*-value**
Pain[n(%)][a]	Mild	37 (88.1%)	27 (67.5%)	.101
	Moderate	4 (9.5%)	10 (25.0%)	
	Severe	1 (2.4%)	3 (7.5%)	

Figure 1 : CONSORT 2010 Flow Diagram



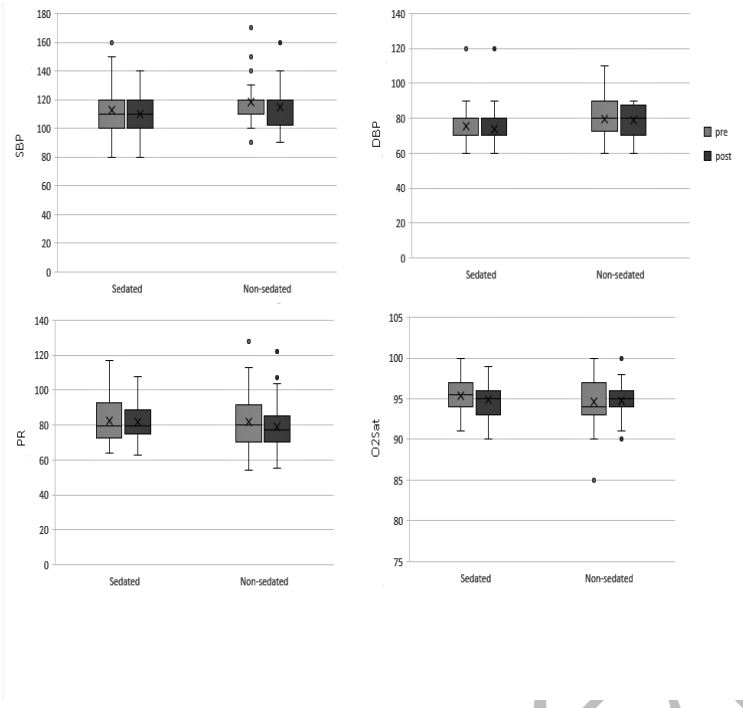
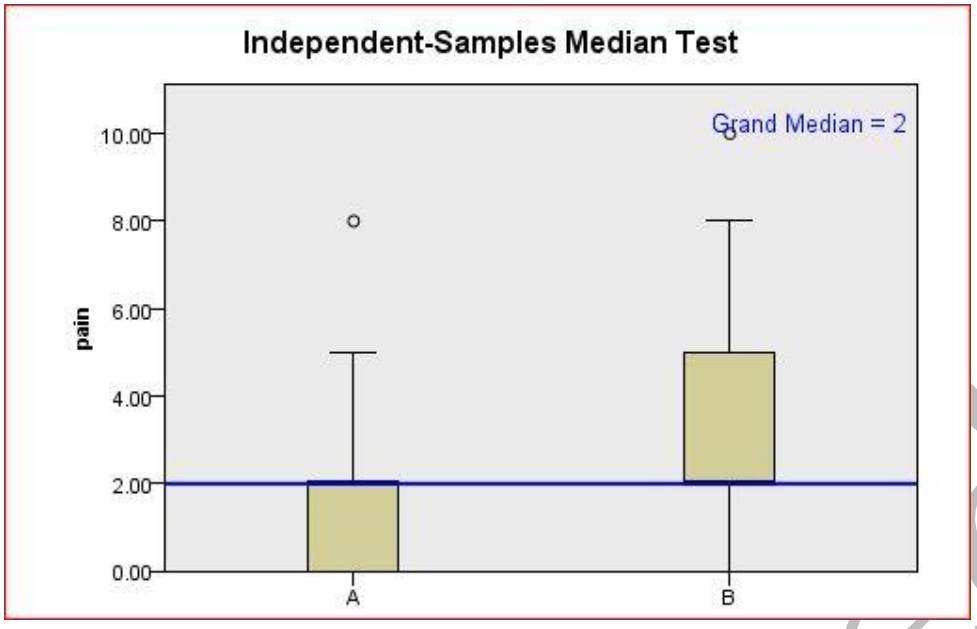


Figure 2: Comparison of changes in physiological parameters in two groups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Grand Median = 2
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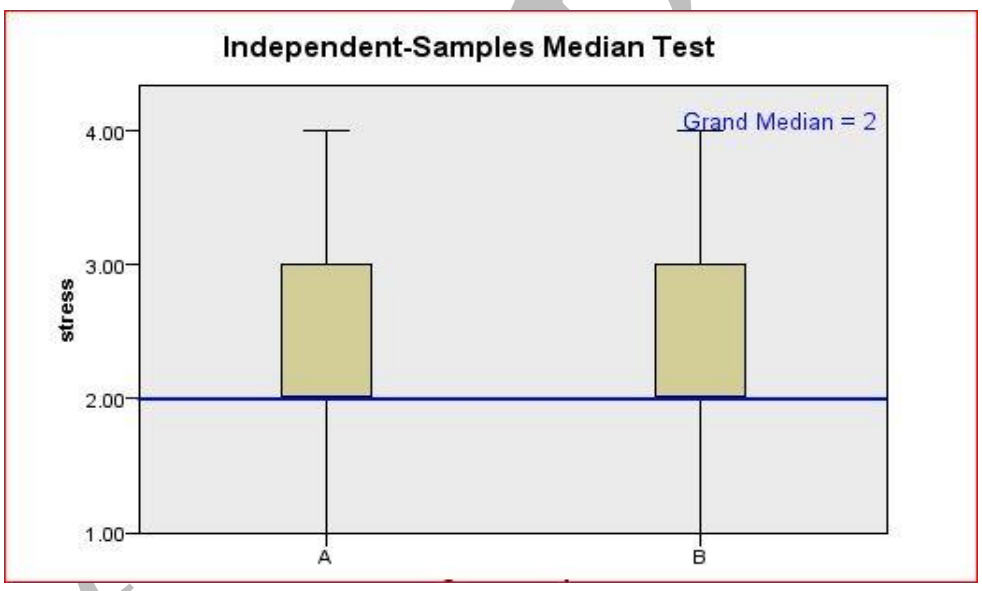
8.00
6.00
4.00
2.00
0.00
A
B

1


Independent-Samples Median Test
Grand Median = 2
stress
4.00
3.00
2.00
1.00
A
B

2

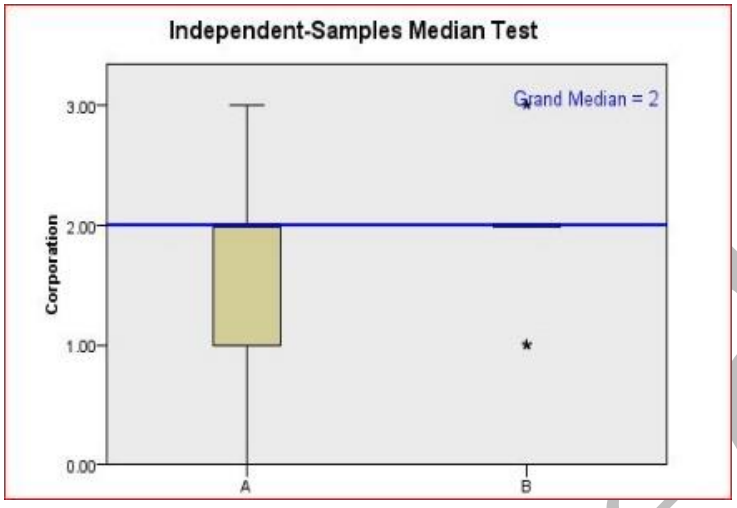


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Figure 3. Comparison of pain(1), stress(2)and corporation(3) scores between sedated (A) and non-sedated (B) groups