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CLINICALLY SIGNIFICANT EFFECTS OF ULTRASOUND GUIDED TRANSVERSAL ABDOMINAL PLANE BLOCK IN OPERATIVE GYNECOLOGY

AUTHOR'S SUMMARY

Dissertation work for awarding the educational and scientific degree "Doctor"
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The dissertation is written on 177 pages, illustrated with 108 figures and 49 tables.

The bibliography contains a total number of 174 sources, 15 in cyrillic and 159 in latin.

All the research work for the dissertation is conducted in University hospital for obstetrics and gynecology „Maichin dom", Sofia, Bulgaria

The dissertation work was discussed at a meeting of the scientific council at the Department of anesthesia and intensive care - Medical university – Sofia and is directed for an official defence before a scientific jury

List of abbreviations

AH- Abdominal hysterectomy
ANI- Analgesia Nociception Index
ASA- American society of anesthesiologists
BiS- Bispectral index
CONSORT- Consolidated Standards of Reporting Trials
DN- Douleur neuropathique
EPCA- Epidural Patient-controlled Analgesia
$EtCO_2$- End-tidal CO_2
FDA- Food and drug administration
GABA- Gamma-aminobutyric acid
IASP- International Association of study of pain
ICU- intensive care unit
LH- laparoscopic hysterectomy
mOAE- Musculus obliqus abdomis externus
mOAI- Musculus obliquus abdominis internus
mTA- Musculus transversus abdominis
NMDA- N-methyl-d-aspartate
NOL- Nociception level index
PCA- Patient controlled analgesia
RH- Robotic hysterectomy
TAP- Transversal abdominal plane
WDR- Wide dynamic range (neurons)

Contents

I. Introduction

Anesthesiology and intensive care is a modern and constantly developing medical speciality. During the recent years, new opportunities have appeared in the realization of different anesthetic techniques related to general and locoregional anesthesia. An example of a recently introduced advantage in anesthesiology is the daily practical use of ultrasound equipment to visualize the process of performing peripheral nerve blocks.

The first regional technics of anesthesia, such as peripheral nerve blocks, were performed blindly. Complications during such manipulations were frequent. The success rate and safety for the patient were low. Introduction of electrical neurostimulation facilitated the identification of peripheral nerves and nerve plexuses. This improved the practice of local technics for pain relief and ameliorated sensory-motor impulse blockade, but did not protect the underlying anatomical structures from any possible unintentional damage.

The modern way to achieve optimal results in the conditions of maximum security in the practice of peripheral nerve blocks consists on implementation under ultrasound control. The discovery of ultrasound and the piezoelectric effect date back to the end of the 19th century. Their first practical application was in the echolocation of ships. They were used to prevent a potential collision of the vessels and were called SONAR (Sound Navigation and Ranging). One of the pioneers in the use of ultrasound for medical purposes is the Austrian psychiatrist and neurologist Karl Dussik. In 1937, he made attempts to examine the brain through the cranial bones, but did not achieve any satisfactory results. Later, technical amelioration of the ultrasound machines, led to their mass application in obstetrics, gynecology and other clinical disciplines. The use of ultrasound by anesthesiologists for the purposes of visualization of the structures of the peripheral nervous system date since the late eighties of the XXth century. Nowadays, almost all reversible peripheral nerve blockades are performed under ultrasound control. The use of ultrasound for regional anesthesia techniques can be referred to as one of the most significant events in the modern development of anesthesiology. The ultrasound machine shows in depth both the tissues and the needle used for locoregional anesthesia. This enables the realization and visualization of peripheral nerve block in real time. One has a visual control over the whole process of blockade. It begins with the puncture of the skin, follows the passage of the needle through the anatomical structures until it reaches the desired nerves and ends with the injection of the local anesthetic products. In this way, various locoregional techniques are carried out reliably, safely and steady for the patient. The ultrasound machine allows the performance of new technics that are practically impossible to execute in a blind

way. In most countries with developed modern medicine, the use of high-tech ultrasound navigation for locoregional anesthesia is a medical standard.

Hysterectomy is one of the most popular interventions in operative gynecology. The indications for its performance are various. The approach for removal of the uterine body is abdominal, vaginal, microinvasive or combined. Regardless of the surgical technique, hysterectomy causes acute and severe perioperative pain. Only high quality analgesia allows the surgical intervention to be carried out and reduces the patient's suffering. Thus the patient's satisfaction is increased and hospital stay is shortened. This is an important economic factor and a sign of healthcare quality. Good analgesia leads to earlier movement of the operated patients and reduces the risk of development of chronic pain syndromes.

Nowadays the low-quality postoperative pain control is inadmissible from a clinical, medicoethical, and last but not least importance-financial point of view.

Considering the multiple aspects of pain perception, we designed and conducted the present prospective randomized clinical trial. For the first time in Bulgaria, our team studied the effectiveness of ultrasound-guided peripheral blockade in transversal abdominal plane on perioperative analgesia after removal of the uterine body via three different types of operative approach - abdominal hysterectomy (AH), laparoscopic hysterectomy (LH) and robotic hysterectomy (RH).

II. Objective and tasks

Objective

The primary objective of this dissertation was to evaluate the analgesic clinical effect of TAP block application, under ultrasound guidance, according to clinical indicators and international pain scales after abdominal, laparoscopic or robotic hysterectomy.

Tasks

1. Comparison of postoperative Morphine consumption between the studied groups.
2. Comparison of intraoperative Fentanyl consumption between the studied groups.
3. Evaluation of subjective static pain level on VNS (verbal numeric scale) during the first 24 postoperative hours.
4. Evaluation of subjective dynamic pain level on VNS (verbal numeric scale) during the first 24 postoperative hours.
5. Analysis of the incidence of complications as a consequence of Morphine use- nausea and vomiting, troubles in conscience and appearance of pruritus during the first 24 postoperative hours.
6. Evaluation of "preventive" effect of TAP block by searching the signs of central sensitization syndrome (appearance of neuropathic pain) on the 30^{-th}-45^{-th} postoperative day.

III. Matherials and methods

Study design

The study was carried out in accordance to bulgarian and international requirements for good practice in clinical trials. The anonymity of the patients has been preserved and their personal information protected. The preparation of protocols is in accordance with the Declaration of Helsinki principles, the requirements for good clinical and laboratory practice, and in accordance with the current legislation of Republic Bulgaria. All participants in the study signed an informed consent.

The recruitment of patients started in the middle of 2017 and ended December 2021. Over a period of about 4 years, we studied 182 patients admitted for AH, LH or RH. 26 of the patients dropped out. We performed statistical analysis on 156 cases, (fig.1).

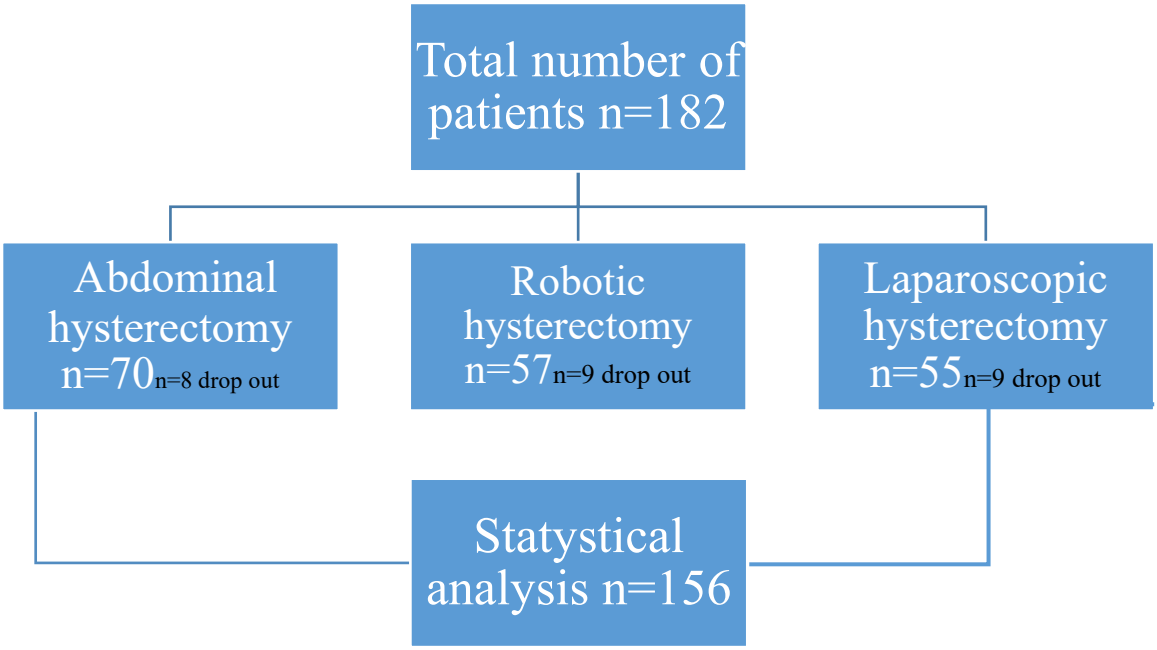


Figure1 Schematic view of total number of patients included in the dissertation.

Patients and groups

We divided the patients into three big, independent groups according to the surgical access used to perform the hysterectomy (fig.2):

- Laparotomy via Pfannenstiel
- Laparoscopic hysterectomy
- Robot assisted hysterectomy

Every group was separated in a TAP block group and a control one (fig.2):

- **TAP block group**: patients, that receive a pre-operative bilateral TAP block with Ropivacain0.5% in a dose of 2.5mg/kg. The calculated amount is diluted to 40ml (20 ml for left and right body side)
- **Control group**: patients without any local blockade

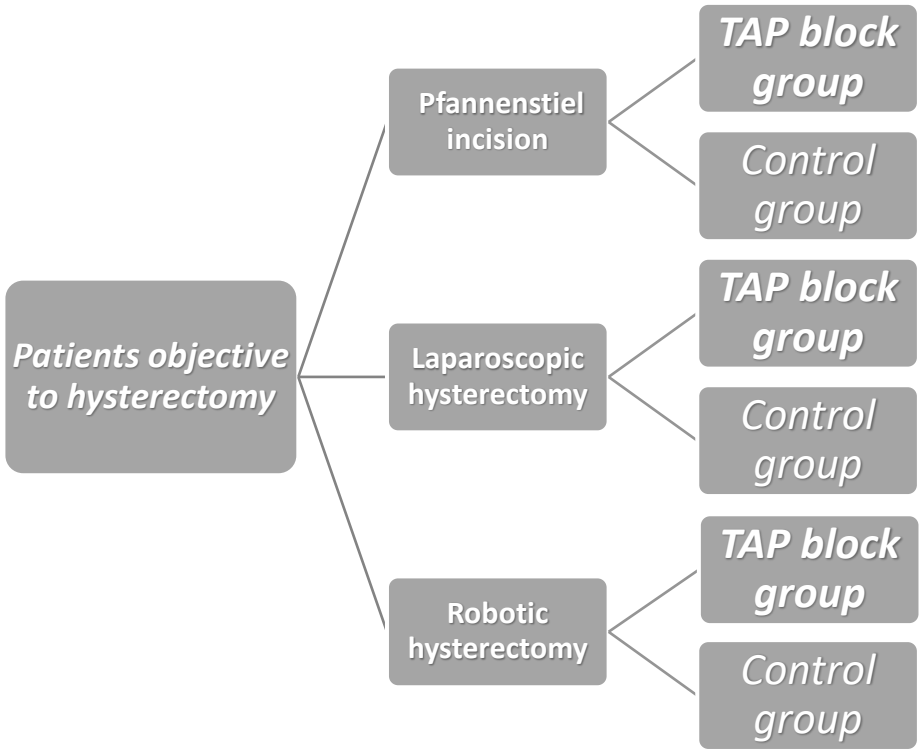


Figure2 Schematic view of study design according to surgical approach- AH, LH, RH. Every group separates into two smaller groups- TAP block group and a control one.

The participants with an even consecutive number in the trial receive TAP block, where as the participants with an odd consecutive number in the trial do not receive any local blockade and form the control group.

The statistical analysis is accomplished only between the patients with the same type of surgery i.e. AH, LH, RH.

The participants were selected according to inclusion and exclusion criteria. The demographic data of all the participants was registered.

Technical information

Each participant received a standardized general anesthetic. Before the beginning of the surgery, an ultrasound guided bilateral TAP block with Ropivacaine 0.5% in a dose of 2.5mg/kg (to a maximal total dose of 200 mg) was applied for the patients of the corresponding group.

The calculated amount of Ropivacaine 0.5% for each patient was diluted up to 40 mL with NaCl 0.9% (20 mL for the left and 20 mL for the right side). The needle insertion approach was lateral. We used an ultrasound BENQ T3300 device with a linear probe (6-13 MHz) and a 0.7 x 80 mm echogenic needle Ultraplex (B. Braun ®). Following a verification of the exact position of the needle tip, the calculated volume of local anesthetic was injected into the TAP on the left and the right body side (fig.3). The control group, as mentioned above, did not receive any local blockade. At the admission in the intensive care unit, all the patients received a loading dose of 0.05 mg/kg intravenous morphine. A patient controlled analgesia medical device (Graseby PCA pump, model 3300, with placed CE mark showing it has passed a conformity assessment) was attached to every participant, with the following setting: bolus of morphine at demand - 1 mg, lockout time - 10min, without any dose-limit for 24 h. The pain was assessed at rest and in motion (knee flexion) on. Postoperative nausea and vomiting (PONV) were registered on a four-point categorical scale (0=abscence, 1=mild, 2=moderate, 3=severe). At the 24th post-surgical hour the PCA was disconnected and the total amount of morphine consumption was registered.

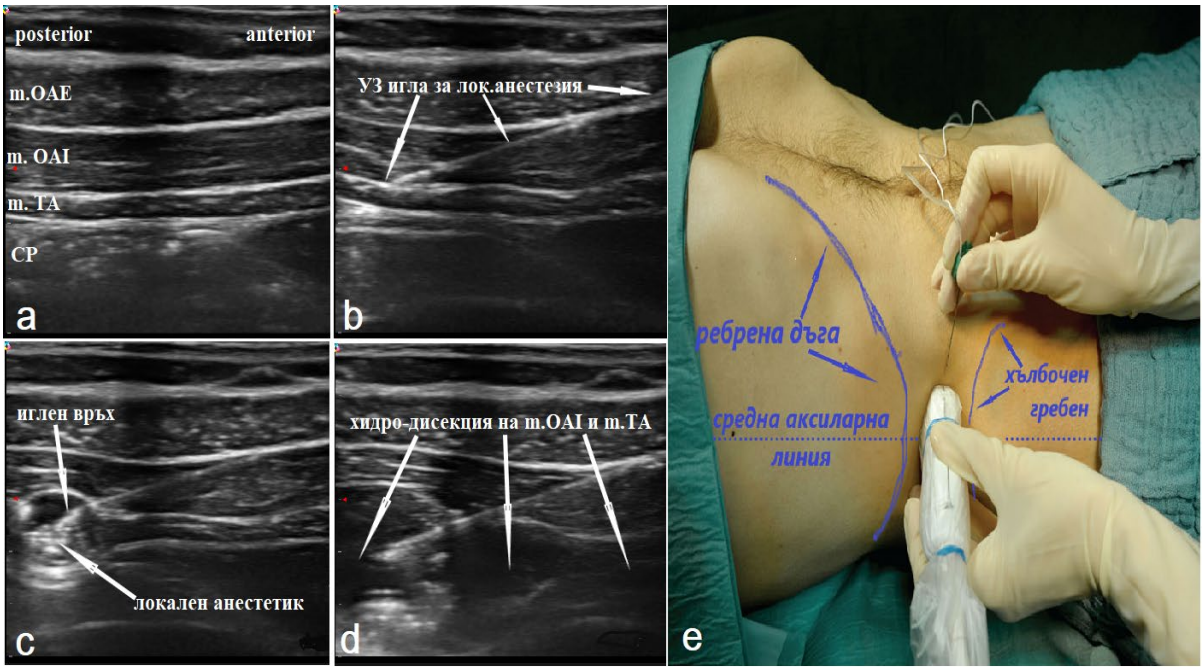


Figure3 We have presented a view of pre-marked external body anatomical landmarks relative to the transducer position and an echographic capture of the consequent stages of the TAP block in real time. The access we use is lateral.

***a**.Ultrasound image of anatomy of anterolateral abdominal wall: mOEA (m. obliquus externus abdominis), mOIA (m. obliquus internus abdominis), mTA (m. transversus abdominis), CP (cavum peritonealis).*

***b**. Image of hyper echogenic needle for local anesthesia in whole length.*

***c**. Hydrolocalosation of needle tip.*

***d**. Hydro dissection of the muscles of abdominal wall.*

***e**. Position of US probe and site of punction.*

During the first 24 postoperative hours in the Intensive care unit, the following patients' data was registered:

1. VNS results for static pain at six different time moments—the admission in the ICU (0 h), at the 3rd, 6th, 12th and 24th postsurgical hour. (fig.4).
2. VNS results for dynamic pain at six different time moments—the admission in the ICU (0 h), at the 3rd, 6th, 12th and 24th postsurgical hour (fig.4).
3. Ramsay sedation score at 0, 3rd,6th,12th,24th postsurgical hour (fig.5).
4. Appearance of opioid side effects - postoperative nausea and vomiting (PONV), and pruritus were registered. (fig.5).

Endpoints

Primary endpoint

The primary endpoint was the total 24-hour postoperative morphine consumption.

Secondary endpoints:

1. Fentanyl consumption during the intervention.
2. Morphine consumption for the first 12 postoperative hours.
3. Quality of analgesia according to VNS results for static pain.
4. Quality of analgesia according to VNS results for dynamic pain.
5. Evaluation of Ramsay sedation score (fig.5).
6. Presence of opioid side effects- PONV, pruritus (fig.5).
7. Evaluation of DN4 (from French- Douleur Neuropathique) between the 30th -45th postoperative day, in the group of patients with AH.

Име:
Дата:
Час на пост. в Реа:

0	2	4	6	8	10
НЯМА БОЛКА	СЛАБА БОЛКА	СРЕДНА БОЛКА	СИЛНА БОЛКА	МНОГО СИЛНА БОЛКА	НЕТЪРПИМА БОЛКА

Следоперативен час	Статична Болка	Динамична болка
0ч.		
3ч.		
6ч.		
12ч.		
24ч.		

Figure 4 The form was created by our team in order to apply the individual data assesesment of the patients for static and dynamic pain. We used the international Verbal Numeric Scale and adapted it in Bulgarian language.

Оценка на странични ефекти на опиати

СКАЛА НА РАМЗИ ЗА СЕДАЦИЯ

1. Неспокойна, ажитирана, угрижена
2. Кооперативна, ориентирана, спокойна
3. Отговаря само на команди
4. Оживен отговор при леко почукване по глабелата или при силно повикване
5. Муден отговор при леко почукване по глабелата или при силно повикване
6. Без отговор при отговор при леко почукване по глабелата или при силно повикване

0- Липса на гадене
1- Слабо гадене
2- Умерено гадене
3- Тежко гадене

Вербална дескриптивна скала за оценка на след- оперативно гадене и повръщане

След-оперативен час	Скала на Рамзи	Гадене & повръщане	Сърбежи
0ч.			
3ч.			
6ч.			
12ч.			
24ч.			

Figure 5 The form was created by our team in order to register the opioid side effects.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 19 (www.IBM.com). An independent samples t-test was used for continuous variables and the values were presented as means with standard deviations (±SD). To evaluate the normality of distribution, the Shapiro-Wilk test was used. The nonparametric data were analyzed by descriptive statistics and the values were presented as medians and interquartile range. A Mann–Whitney U-test was performed to determine the level of significance. Two-way mixed ANOVA stat. test was applied to evaluate the repeated measures. Differences were considered statistically significant at the $P < 0.05$ level.

The sample size was determined using a nQuery Advisor v.6. Statistical calculator. A previous study on the effect of the TAP block on postoperative analgesia after total abdominal hysterectomy was used for the calculation [Marais & al]. The mean 24-hour morphine consumption in this study was 23 ± 7 mg. We accepted that decrease of 25% in absolute morphine consumption is clinically relevant. With $\alpha = 0.05$ and $\beta = 0.2$, a minimum of 23 patients in each group were required.

The statistical study proceeds in the following sequence:

- statistical observation
- statistical grouping
- statistical analysis

During statistical monitoring, the units included in the study are registered. The data of interest for the specific statistical study are reported. Nominal parameters are turned in a numerical code to each specific nominal value. Ordinal marks are naturally digitized. The statistical grouping performs a distribution of the units. The initial group selection was made according to whether the intervention was performed by Pfannenstiel incision, laparoscopic hysterectomy, or robotic hysterectomy. Each group is independently statistically examined, from the two other groups, for the effect of the TAP block. Statistical analysis, as the final phase of statistical research, uses different statistical tests for obtaining aggregated data and its interpretation. A descriptive statistical analysis was performed.

For analysis of up to two unrelated, quantitative, dependent variables, grouped by a nominal independent variable (factor), the Student's t- test was used, like Independent Sample t-test (in the case of homogeneity of variations) or the Welch-t test (in the case of disturbed homogeneity of variations). These parametric tests are highly accurate, requiring a minimal number of patients and a normal distribution of the variable. Before conducting them, the data is inspected using box plots for the presence of extreme values (outliers). The latter are subject

to removal. The normality of the distribution is established by graphical methods (visual inspection of histogram, Q-Q plots) and numerical methods—Shapiro-Wilk test. In the Shapiro-Wilk test, a significance level of 0.05 is set. The null hypothesis of this test states that the distribution of the variables in the populations is normal. Therefore, at a value of $\alpha \geq 0.05$, the null hypothesis cannot be rejected and the alternative hypothesis cannot be accepted. The distribution of the data is assumed to be normal.

To assess the homogeneity of variations in the populations of the studied groups, Levene's test is applied. This test assumes the null hypothesis that the variances within the groups are the same. A significance level of 0.05 is accepted. At a value of $\alpha \geq 0.05$, the null hypothesis cannot be rejected and the alternative hypothesis cannot be accepted. We assume that homogeneity of variance is present between the two populations.

The results of the parametric tests are presented as mean ± standard deviation (mean ± SD), mean difference and 95% confidence interval limits (mean difference & CI 95%).

In cases where the analysis of two quantitative variables does not meet the requirements to carry out a parametric test (violated normality of the distribution) is required, a non-parametric test of Mann-Whitney U test is used. The shape of the distribution of the data within the groups in this test is assessed by visual inspection of the population pyramids. If the shape of their distribution is similar, the medians are compared. If their form is different, a comparison of the mean rank sums is performed.

When comparing the group differences of ordinal dependent variables, the non-parametric Mann-Whitney test was applied. Its interpretation is carried out in the manner described above.

Cross-tabulations and the $\chi 2$ test of homogeneity were applied to determine differences in homogeneity of distribution of multinomial variables between the groups. When there are no criteria for its implementation (minimum number of 5 units in each cell of the crosstab), Fisher's exact (2xR) test is applied.

The confidence and significance level for all statistical tests within the study was assumed to be $(1- \alpha)=0.95$ at $\alpha=0.05$ (5% error).

IV. Results

Statistical analysis of the patients with abdominal hysterectomy via Pfannenstiel

Study design

Seventy women with AH were assessed for eligibility in the trial and all of them were enrolled in the study. For different reasons eight patients dropped out. Overall, 62 patients completed the study and were analyzed (fig.6).

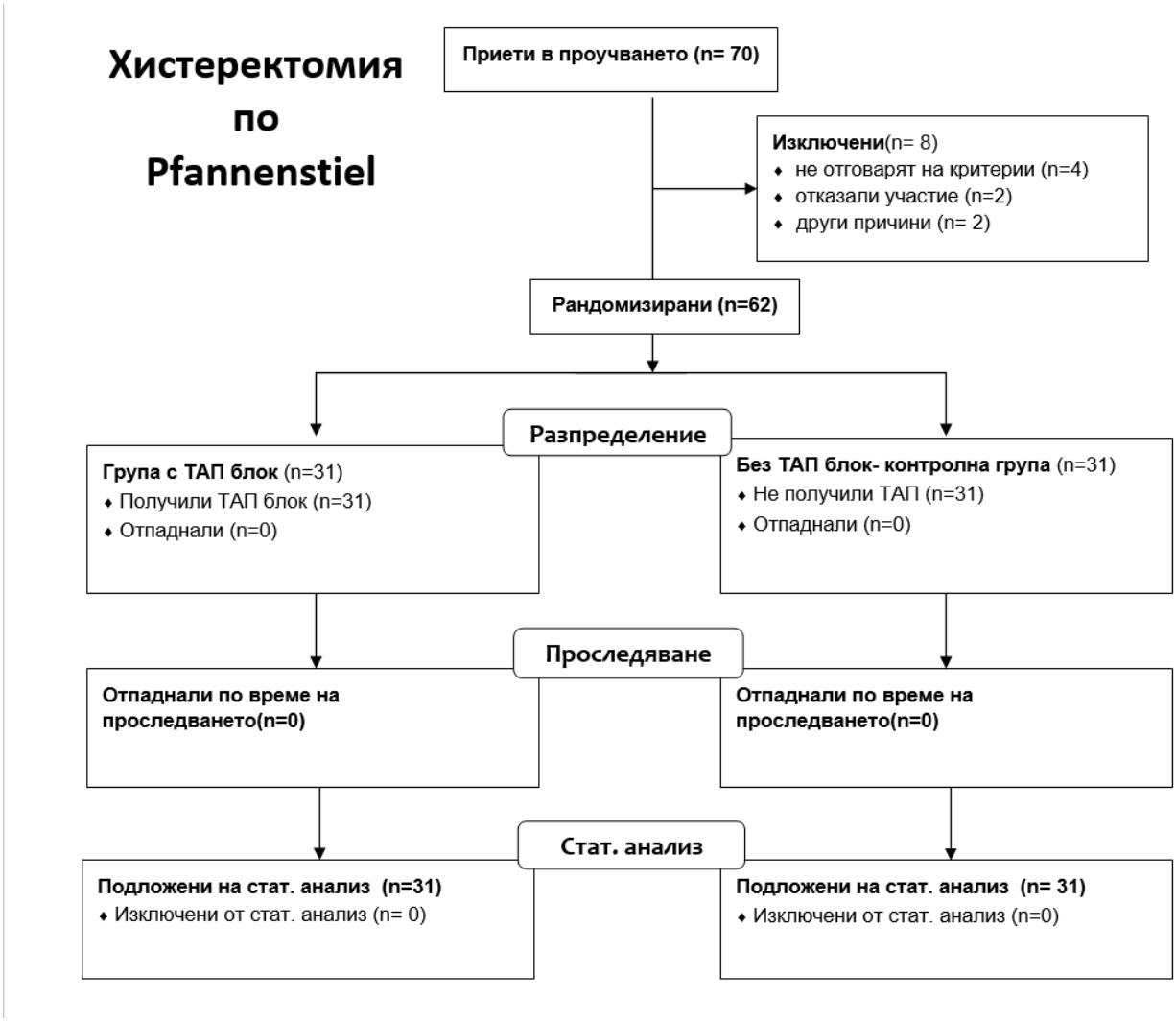


Figure6 CONSORT diagram of study design of AH group

Patients' demographic characteristics

No statistically significant differences were observed between the two groups in terms of age, weight, height, BMI, ASA grade and the time of surgery (table1).

Table 1 Patients' demographic characteristics of AH group.

Group	TAP block group	Control group	*P significance*
Age(years)	59.1±4.9	61.3±5.6	*p=0.119*
BMI	25.4±3.4	24.7±2	*p=0.362*
Operative time (min)	108.9±8.8	112.9±8.4	*p=0.425*
ASA			*p=0.879*

Fentanyl consumption during surgery

The mean intraoperative consumption of fentanyl was higher in the control group (213µg±20µg), than in the TAP block group (158µg±21µg) (fig.7). The difference is statistically significant U=30, z= -6.486, *p=0* Mann-Whitney U test (table2).

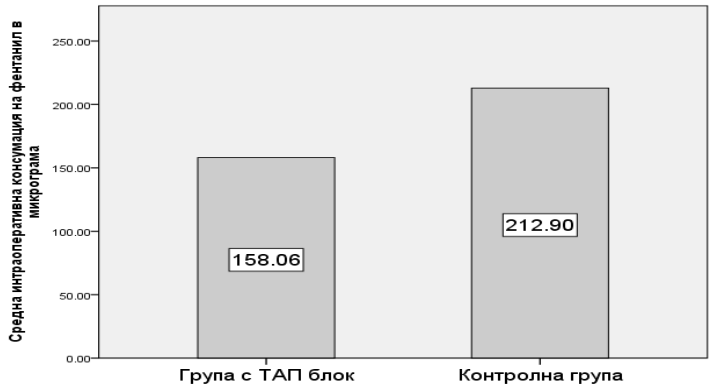


Figure 7 Mean Fentanyl consumption in µg of AH group

Table 2 Mean rank and sum of ranks of Fentanyl consumption of AH group

	TAP block	N	Mean rank	Sum of ranks
	YES	31	16.97	526.00
	NO	31	46.03	1427.00
	Total	62		

Morphine consumption

Morphine loading dose

The mean amount of morphine, used for loading dose in ICU was higher in the control group (3.5±0.6mg), than in the TAP block group, (3.3±0.6mg). The difference of 0.2±0.1mg has no statistical significance (95% CI -0.52— 0, 68, t(60)= -1.535, *p=0.130*), (fig.8).

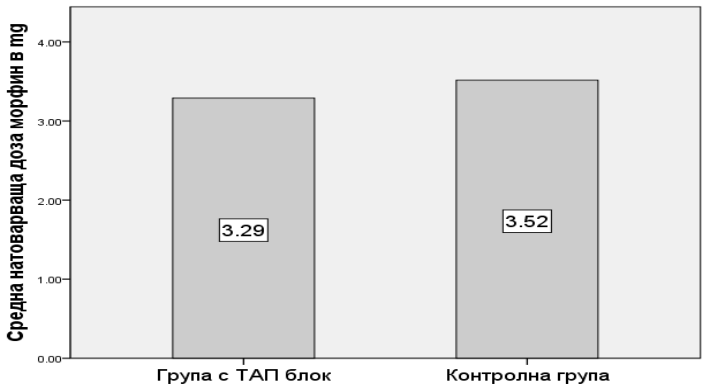


Figure 8 Mean loading dose of Morphine of AH group.

Morphine consumption for the first 12 postoperative hours

The mean cumulative consumption of morphine for the first 12 postoperative hours was higher in the control group (12.7±4.6mg), than in the TAP block group (9.3±2.8 mg), (fig.9). A statistically significant difference of 3.5±0.9mg (95% CI -5.44— - 1.527, t(49.5)= -3.578, *p=0.001*) was observed.

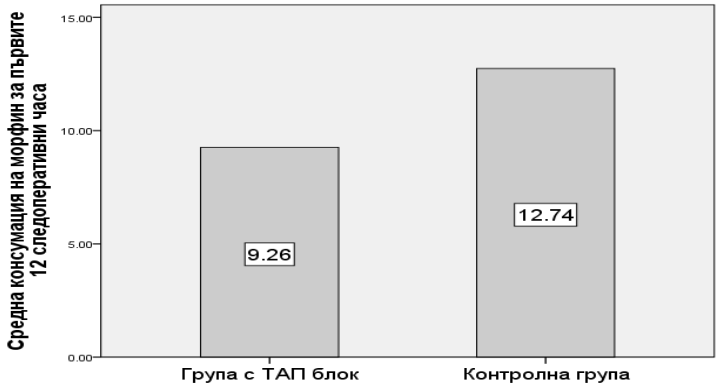


Figure 9 Mean Morphine consumption in mg 0-12-th postoperative hour of AH group

Morphine consumption for the second 12 postoperative hours

The mean cumulative consumption of morphine for the second 12 postoperative hours was higher in the control group (6.7±2.3mg), than in the TAP block group (2.3±1.4mg), (fig.10). A statistically significant difference of 4.5±0.5mg (95% CI -5.469— - 3.498, t(50.020)= -9.139, *p=0*) was observed.

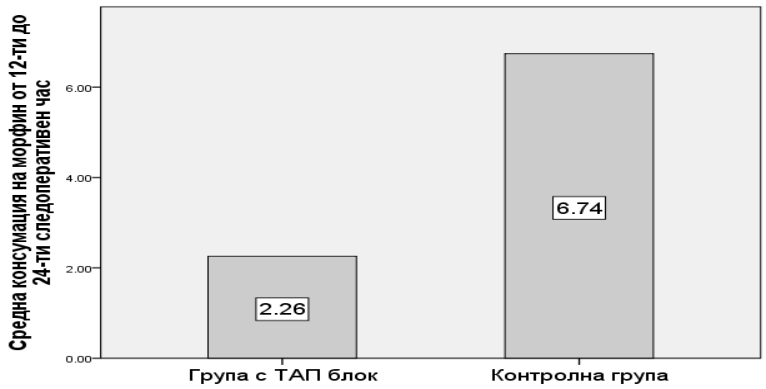


Figure 10 Mean Morphine consumption in mg 12-th-24-th postoperative hour of AH group

Cumulative 24 hours Morphine consumption

The mean cumulative consumption of morphine for the first 24 postoperative hours was higher in the control group, (23±6.4mg), than in the TAP block group (14.8±4 mg). A statistically significant difference of 8.2mg±1.4mg (95% CI -10.901— - 5.485, t(49.8)= -6.052, *p=0*) was observed (fig.11).

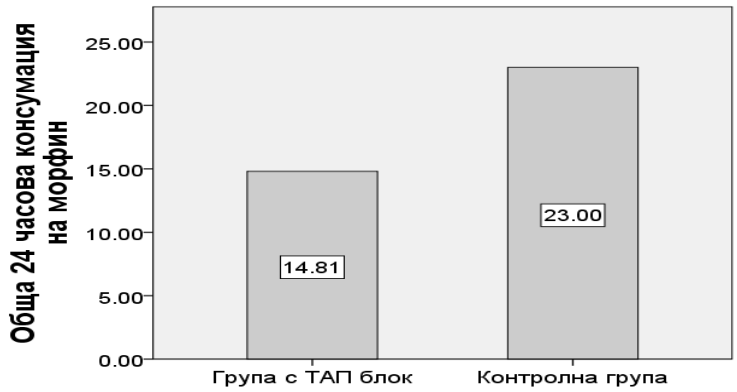
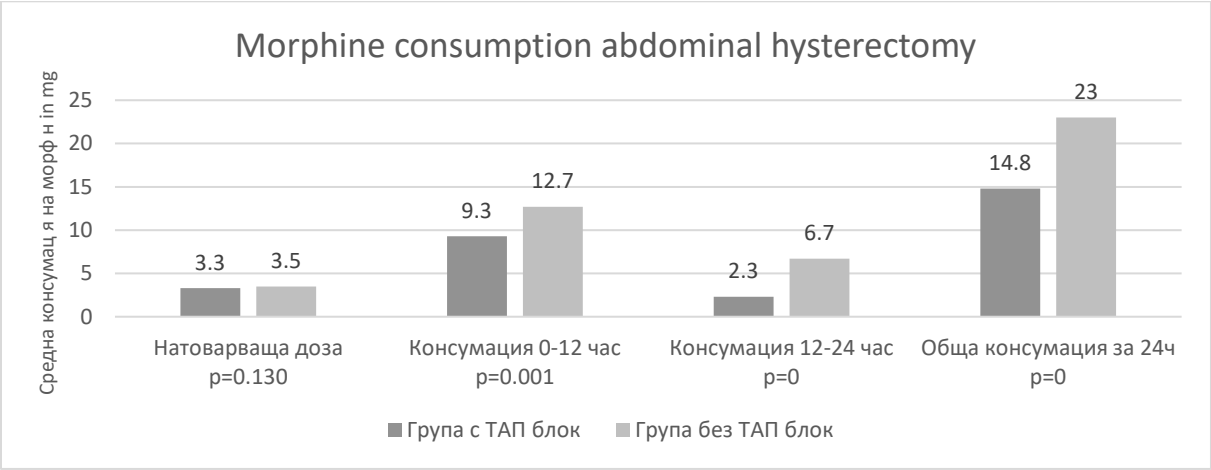


Figure 11 Mean total Morphine consumption for 24 hours period of AH group.

Discussion about Morphine consumption

The control group presents consistently higher values of opiate consumption compared to the TAP block group. This mean difference of Morphine consumption between the groups is statistically significant for both the first (p=0.001) and the second (p=0) half of the first 24 postoperative hours. The mean total 24-hour morphine consumption also demonstrated a statistically significant difference between groups (p=0), (table3).

Table 3



Verbal Numeric Scale for static pain evaluation.

Mann-Whitney U test

Static pain 0 hour

The control group presents statistically significant higher values of mean rank and median (mean rank=40.63, median=6), than the TAP block group (mean rank= 22.37, median=3), U=197.5, z= -4.029, p=0.

Static pain 3^{-th} hour

The values of mean rank and median of the control group (mean rank=39.60, median=6) are statistically significant higher than TAP block group(mean rank=23.40 , median=4), U=229.5, z= -3.607, *p=0*.

Static pain 6^{-th} hour

The control group presents statistically significant higher values of mean rank and median (mean rank=41.55, median=6), than the TAP block group (mean rank=21.45 , median=4), U=169, z= -4.485, *p=0*.

Static pain 12^{-th} hour

The control group presents statistically significant higher values of mean rank and median (mean rank=41.13, median=5), than the TAP block group (mean rank=21.87 , median=4), U=182, z= -4.396, *p=0*

Static pain 24^{-th} hour

The control group presents statistically significant higher values of mean rank and median (mean rank=42.53, median=3), than the TAP block group (mean rank=20.47, median=2), U=138.5, z= -4.968, *p=0*

Independent sample T test

Static pain 0 hour

The mean values of control group VNS are higher (5.7±1.4), compared to TAP block group values(3.8±1.8). The mean difference of 1.9±0.4 is statistically significant (95% CI -2.767— -1.103, t(60)= -4.655, *p=0*).

Static pain 3-th hour

The mean values of control group VNS are higher (6±1.3), compared to TAP block group values (4.5±1.5). The mean difference of 1.45±0.36 is statistically significant (95% CI -2.166— -0.736, t(60)= -4.063, p=0).

Static pain 6-th hour

The mean values of control group VNS are higher (5.8±1.2), compared to TAP block group values (3.9±1.6). The mean difference of 1.8±0.35 is statistically significant (95% CI -2.555— -1.103, t(60)= -1.122, *p=0*).

Static pain 12-th hour

The mean values of control group VNS are higher (5±0.8), compared to TAP block group values (3.6±1.2). The mean difference of 1.3±0.25 is statistically significant (95% CI -1.832— -0.812, t(50.4)= -5.204, *p=0*).

Static pain 24-th hour

The mean values of control group VNS are higher (3.6±0.8), compared to TAP block group values (2.2±1). The mean difference of 1.4±0.2 is statistically significant (95% CI -1.8912— -1.103, t(60)= -6.017, *p=0*).

Discussion comment

Both, TAP block and the control group, have the highest average values of VNS at the third postoperative hour. On the 6th, 12th and 24th postoperative hours, these values progressively decrease. TAP block group demonstrated consistently lower mean VNS values at all time intervals. The group with TAP block has similar values at the 6th and 12th postoperative hour. This could be explained with the exhausted effect of Ropivacain. Regardless of this, the locoregional analgesia led to a better clinical subjective, static, pain indicators than the control group. The difference in the values of VNS between the groups, assessed with a parametric (fig.12) and non-parametric test (table 4) is of statistical significance in all five time intervals. It can be concluded that the TAP block improves clinically the subjective parameters of static pain in Pfannenstiel hysterectomy.

Table 4 Sum of ranks and mean ranks of values of VNS for static pain in different time intervals of AH group.

	TAP block	Count	Mean rank	Sum of ranks
VNS 0h	YES	31	22.37	693.50
	NO	31	40.63	1259.50
	Total	62		
VNS 3h	YES	31	23.40	725.50
	NO	31	39.60	1227.50
	Total	62		
VNS 6h	YES	31	21.45	665.00
	NO	31	41.55	1288.00
	Total	62		
VNS 12h	YES	31	21.87	678.00
	NO	31	41.13	1275.00
	Total	62		
VNS 24h	YES	31	20.47	634.50
	NO	31	42.53	1318.50
	Total	62		

Figure 12 Means of VNS values for static pain in different time moments of AH group.

Verbal Numeric Scale for dynamic pain evaluation.

Mann-Whitney U test

Dynamic pain 0 hour

The control group presents statistically significant higher values of mean rank and median (mean rank=40.03, median=7), than the TAP block group (mean rank= 22.97, median=5), U=216, z= -3.778, *p=0*.

Dynamic pain 3^{-th} hour

The control group presents statistically significant higher values of mean rank and median (mean rank=42.56, median=7) than the TAP block group (mean rank= 20.44, median=5), U=137.5, z= -4.906, *p=0*.

Dynamic pain 6^{-th} hour

The control group presents statistically significant higher values of mean rank and median (mean rank=37.84, median=7), than the TAP block group (mean rank= 25.16, median=5), U=284, z= -2.843, p=0.004.

Dynamic pain 12^{-th} hour

The control group presents higher values of mean rank and median (mean rank=35.32, median=5), than the TAP block group (mean rank= 27.68, median=5), but no statistical significance is observed, U=362, z= -1.737, *p=0.82*.

Dynamic pain 24^{-th} hour

The control group presents statistically significant higher values of mean rank and median (mean rank=37.15, median=4), than the TAP block group (mean rank= 25.85, median=3), U=305.5, z= -2.750, *p=0.006*.

Independent sample T test

Dynamic pain 0 hour

The mean values of control group VNS are higher (6.7±1.2), compared to TAP block group values (4.9±2). The mean difference of 1.8±0.42 is statistically significant (95% CI -2.604— -0.943, t(60)= -4.274, *p*=0).

Dynamic pain 3^{-th} hour

The mean values of control group VNS are higher (7.3±1.2), compared to TAP block group values (5.2±1.4). The mean difference of 2±0.33 is statistically significant (95% CI -2.699— -1.365, t(60)= -6.096, *p=0*).

Dynamic pain 6^{-th} hour

The mean values of control group VNS are higher (6.4±1), compared to TAP block group values (5.1±1.7). The mean difference of 1.3±0.36 is statistically significant (95% CI -1.985— -0.531, t(49.6)= -3.462, *p=0.001*).

Dynamic pain 12^{-th} hour

The mean values of control group VNS are higher (5.3±0.9), compared to TAP block group values (4.7±1.4). The mean difference of 0.6±0.3 is statistically significant (95% CI -1.203— -0.021, t(50.313)= -2.075, *p=0.043*).

Dynamic pain 24^{-th} hour

The mean values of control group VNS are higher (3.9±0.5), compared to TAP block group values (3.3±1.1). The mean difference of 0.6±0.2 is statistically significant (95% CI -1.017— -0.144, t(40.595)= -2.685, *p=0.01*).

Discussion comment

Like static pain VNS values, the values for dynamic pain were highest at the third postoperative hour for the both groups. During the next time intervals, the values of VNS decrease. The TAP block group demonstrated consistently lower, mean VNS values at all time intervals. The difference of VNS values between the groups, evaluated with a parametric (fig. 13) and a non-parametric test (table 5) presents statistical significance in all five time intervals. TAP block leads to clinical improvement in both static and dynamic pain scores after abdominal hysterectomy via Pfannenstiel.

Table 5 Sum of ranks and mean ranks of values of VNS for dynamic pain in different time moments of AH group.

TAP block		Count	Mean rank	Sum of ranks
VNS 0hour	YES	31	22.97	712.00
	NO	31	40.03	1241.00
	Total	62		
VNS 3-th hour	YES	31	20.44	633.50
	NO	31	42.56	1319.50
	Total	62		
VNS 6-th hour	YES	31	25.16	780.00
	NO	31	37.84	1173.00
	Total	62		
VNS 12-th hour	YES	31	27.68	858.00
	NO	31	35.32	1095.00
	Total	62		
VNS 24-th hour	YES	31	25.85	801.50
	NO	31	37.15	1151.50
	Total	62		

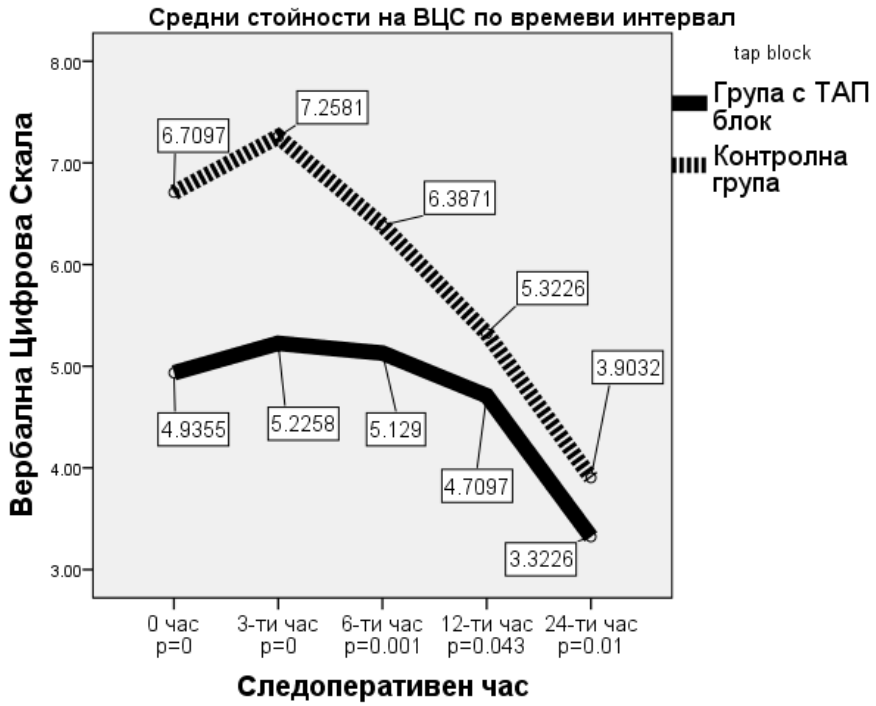


Figure 13 Means of VNS values for dynamic pain in different time moments of AH group.

Incidence of nausea and vomiting

In both groups, there is a predominance of the patients without any symptoms of nausea and vomiting (n=26 in the TAP block group and n=20 in the control group). The patients who showed a mild degree of nausea were, respectively, n=4 in the TAP block group and n=6 in the control group. Moderate nausea occurred in only one patient in the TAP block group (n=1) and in four patients in the control group (n=4). Severe nausea with vomiting was recorded as a symptom in one patient of the control group (n=1), while in the TAP block group no patient was registered (n=0), (table6). The two groups demonstrate the same values of the median (median=1 for the group with TAP block and the control group). The sum of ranks has higher values in the control group (mean rank= 34.74, sum of ranks= 1077), compared to the TAP block group (mean rank= 28.26, sum of ranks= 876). This difference is not statistically significant—U=380, z= -1.847, p=0.065.

Table 6 Count and number of nauseas and vomiting of AH group.

			TAP block		
			YES	NO	TOTAL
	No symptoms	Count	26	20	46
		% in Group	83.9%	64.5%	74.2%
	Mild nauseas	Count	4	6	10
		% in Group	12.9%	19.4%	16.1%
	Moderate nauseas	Count	1	4	5
		% in Group	3.2%	12.9%	8.1%
	Severe nauseas and vomiting	Count	0	1	1
		% in Group	.0%	3.2%	1.6%
	TOTAL	Count	31	31	62
		% in Group	100.0%	100.0%	100.0%

Ramsay sedation score

During all five postoperative time intervals, the patients of both groups demonstrated only value 2 and value 3 on Ramsay sedation scale. We consider the sedation scale scores as a dichotomous dependent variable. Thes statistical comparison was performed with Fisher's exact test 2xR.

Ramsay 0 hour

At the admission to ICU, in both groups, patients with Ramsay sedation score 3 predominate (n=19, 61.3% for the TAP block group and n=20, 64.5%, for the control group) The two groups do not demonstrate statistically significant differences in the distribution ratio of the dichotomous dependent variable "level of consciousness" $\chi 2(1)=0.069$, p=0.793.

Ramsay 3^{-th} hour

On the third postoperative hour in both groups predominate the patients with Ramsay sedation score 2 (n=28, 90.3% for the TAP block group, n=26, 83.9% for the control group). The difference between the groups is not statistically significant, Fisher's exact test 2xR, p=0.707.

Ramsay 6^{-th} hour

In both groups predominate the patients with Ramsay sedation score 2 (n=30, 96.8% for the TAP block group and n=29, 93.5% for the control group).No statistically significant difference is observed, *p=1*.

Ramsay 12-th hour

In both groups predominate the number of patients with Ramsay sedation score 2 (n=30, 96.8% for the TAP block group, n=30, 96.8% for the control group). No statistically significant difference is observed (Fisher's exact test 2xR *p=1*).

Ramsay 24-th hour

All the patients present Ramsay sedation score 2 (n=31, 100% for the TAP block group, n=31, 100% for the control group).

Discussion comment

No significant differences were observed between the TAP block group and the control group in terms of level of consciousness, assessed by the Ramsay sedation scale. TAP block did not lead to a clinically significant effect on the level of consciousness like a opioid side effect.

Pruritus

In the control group 5 patients reported this complication (n=5, 16.1%), where as in the TAP block group 3 (n=3, 9.7%). The difference is not statistically significant (p=0.707 Fisher's exact test 2xR).

Neuroprotective effect of TAP block

Pain in the region of the operative cicatrix

The total number of patients, from both groups, who reported pain symptoms on the thirtieth postoperative day was 24, or 38.7% of all patients. Their distribution by groups is respectively n=11, 35.5% in the TAP block group and n=13, 41.9% in the control group. The difference between the two groups was not statistically significant (p=0.602 $\chi 2$ test for homogeneity).

DN4 results

7 patients in the TAP block group (n=7, or 22.6% of TAP group and 63.6% of all patients reporting pain in TAP block group) demonstrated a total score of 4 points or more on the neuropathic pain questionnaire. In the control group, the number of patients was nine (n=9, which equals to 29% of the control group and 69.2% of the patients who reported pain in the control group). The two groups did not show statistically significant differences in the proportion of patients with neuropathic pain (p= 0.562 $\chi 2$ test for homogeneity).

Statistical analysis of the patients with robotic hysterectomy

Study design

Fifty-seven women with RH were assessed for eligibility in the trial and all of them were enrolled in the study. For different reasons nine patients dropped out. Overall, 48 patients completed the study and were analyzed (fig.14)

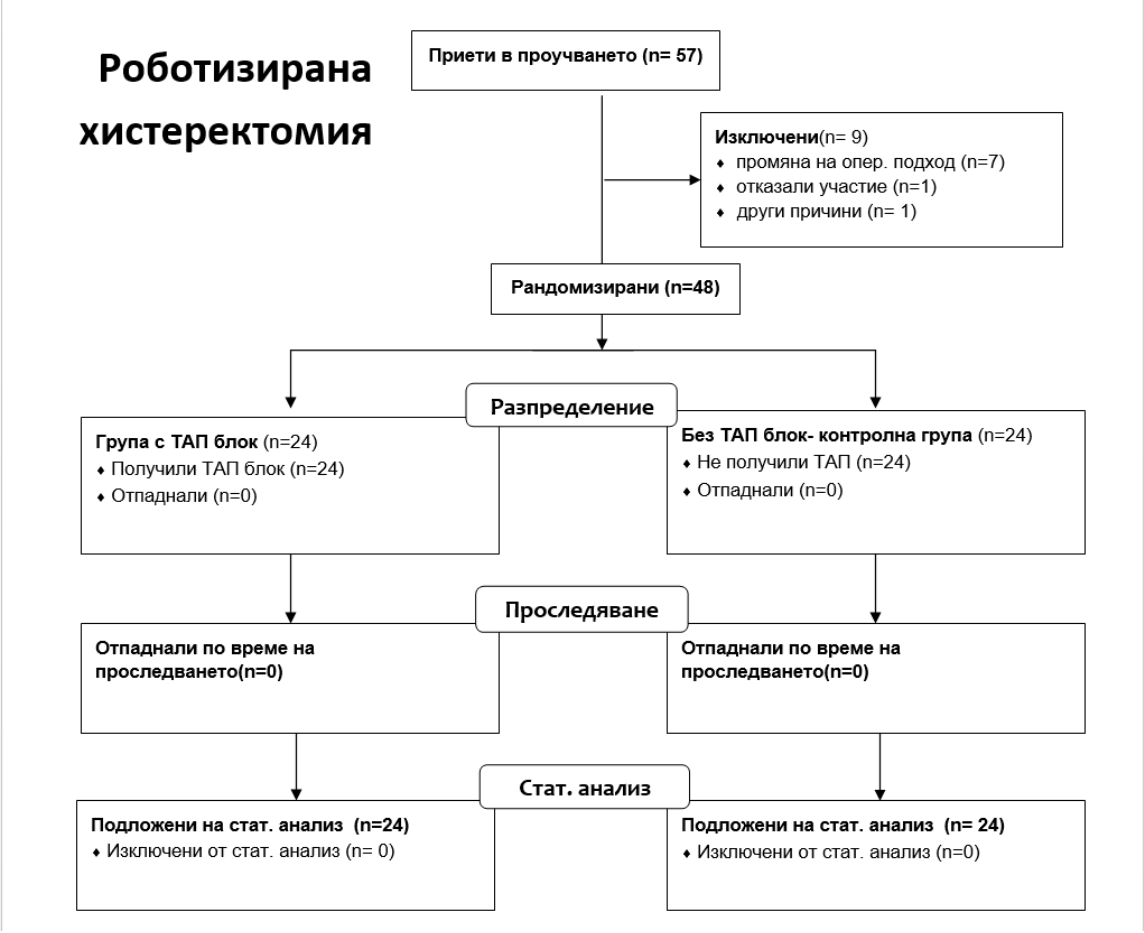


Figure 14 CONSORT diagram of study design of RH

Patients' demographic characteristics

No statistically significant differences were observed between the two groups in terms of age, weight, height, BMI, ASA grade and the time of surgery (table7).

Table 7 Patients' demographic characteristics of RH group.

Group	**TAP block group**	**Control group**	***P significance***
Age(years)	58.8±7.1	60.8±5.6	*p*=0.285
BMI	25.3±2.8	24.9±2.5	*p*=0.536
Operative time (min)	258±9	253±8	*p*=0.089
ASA			*p=0.770*

Fentanyl consumption during surgery

The mean intraoperative consumption of fentanyl was higher in the control group (160µg±22µg), than in the TAP block group (149µg±21µg) (fig.15). The difference is not statistically significant U=204.5, z= -1.909, *p=0.056* Mann-Whitney U test (table8).

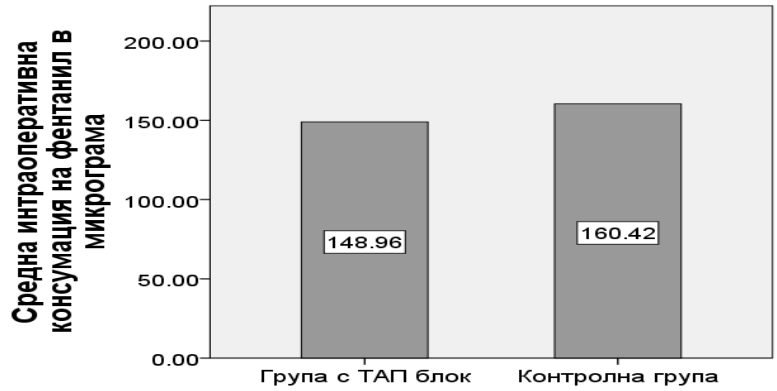


Figure 15 Mean Fentanyl consumption in µg of RH group

Table 8 Mean rank and sum of ranks of Fentanyl consumption of RH group.

	TAP block	N	Mean rank	Sum of ranks
	YES	24	21.02	504.50
	NO	24	27.98	671.50
	Total	48		

Morphine consumption

Loading dose of Morphine

The mean amount of morphine, used for loading dose in ICU was higher in the control group (3.5±0.7mg), than in the TAP block group, (3.46±0.6mg) (fig.16).. The difference of 0.2±0.1mg has no statistical significance. The normality of distribution of values was abused and Mann Whitney U test was used 287.000, z= -0.023, *p=0.981*

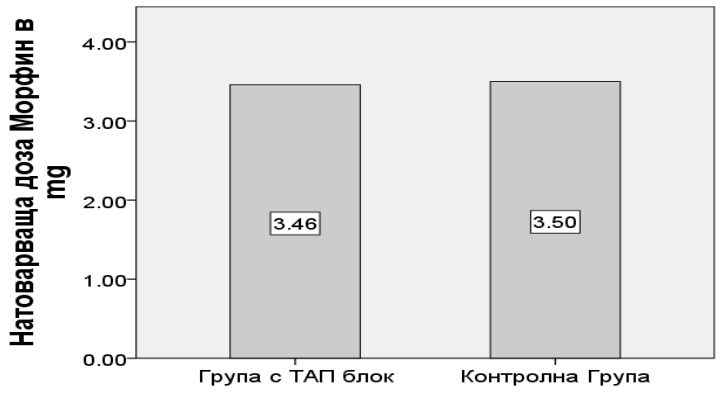


Figure 16 Mean loading dose of Morphine of RH group.

Morphine consumption for the first 12 postoperative hours

The mean cumulative consumption of morphine for the first 12 postoperative hours was higher in the control group (10±3mg), than in the TAP block group (7.8±2.6 mg), (fig.17). A statistically significant difference of 2.2±0.8mg (95% CI -3.82— - 0.51, t(46)= -2.636, *p=0.011*) was observed.

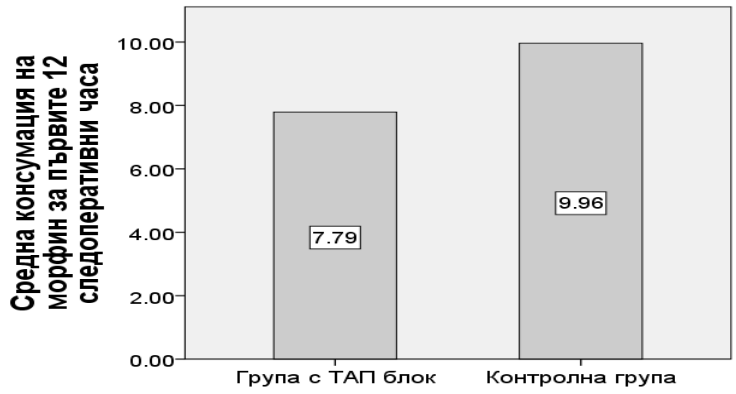


Figure 17 Mean Morphine consumption in mg for 0-12-th postoperative hour RH group.

Morphine consumption for the second 12 postoperative hours

The mean cumulative consumption of morphine for the second 12 postoperative hours was higher in the control group (5.2±1.5mg), than in the TAP block group (2.9±0.8mg), (fig.18). Normality of data distribution is abused and nonparametric Mann-Whitney U test is conducted. The mean difference between the groups presents statistical significance, U=48, z= -5.060, *p=0* (table9).

Table 9 Mean rank and suf of ranks of values of Morphine consumption for the period 12-th-24-th hour RH group.

	TAP block	N	Mean rank	Sum of ranks
	YES	24	14.50	348.00
	NO	24	34.50	828.00
	Total	48		

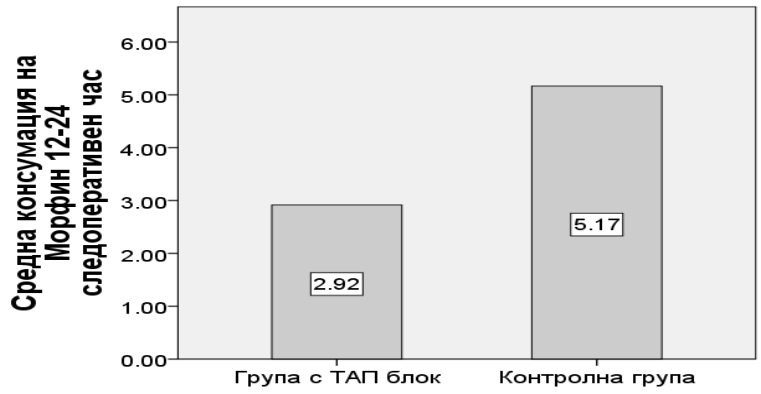


Figure 18 Mean Morphine consumption in mg 12-th -24-th postoperative hour RH group.

Cumulative 24 hours Morphine consumption

The mean cumulative consumption of morphine for the first 24 postoperative hours was higher in the control group, (18.6±4.3mg), than in the TAP block group (14.2±3mg). A statistically significant difference of 4.5mg±1mg (95% CI -6.600— - 2.316, t(46)= -4.190, *p=0*) was observed (fig.19).

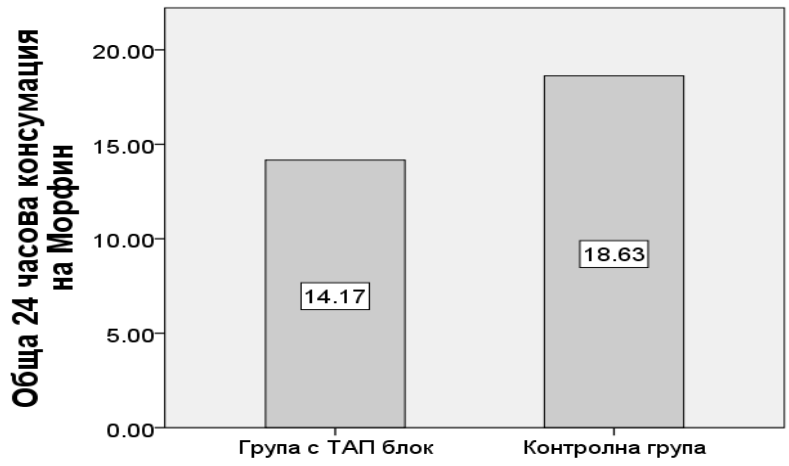
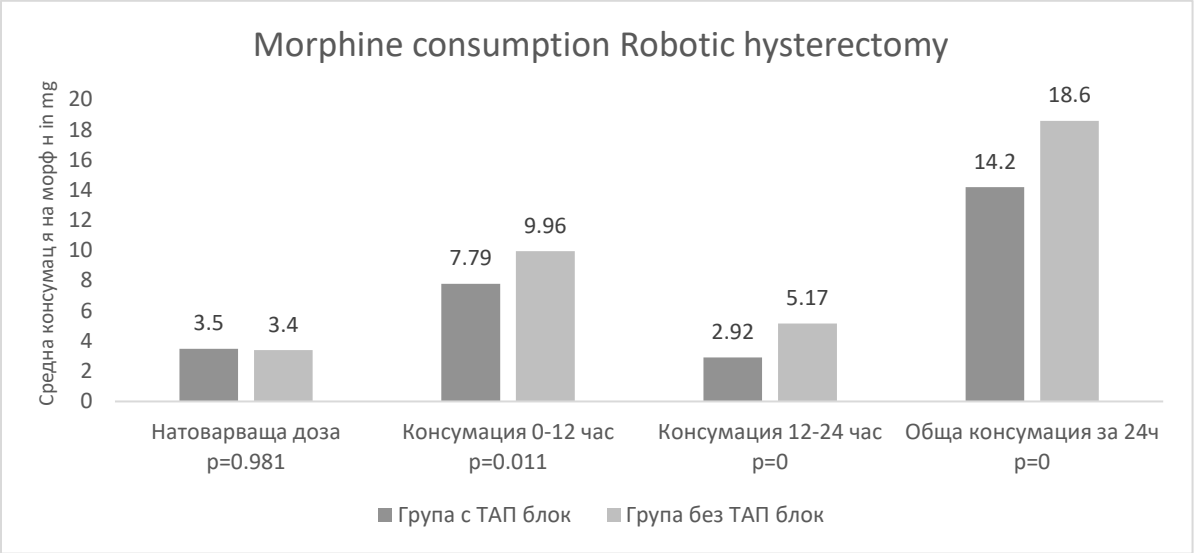


Figure 19 Mean total 24 hours consumption of Morphine RH group.

Discussion about Morphine consumption

The control group presents consistently higher values of opiate consumption compared to the TAP block group. This mean difference of Morphine consumption between the groups is statistically significant for both the first (p=0.011) and the second (p=0) half of the first 24 postoperative hours. The mean total 24-hour morphine consumption also demonstrated a statistically significant difference between groups (p=0), (table10).

Table 10



Verbal Numeric Scale for static pain evaluation.

Mann-Whitney U test

Static pain 0 h

The control group presents statistically significant higher values of mean rank and median (mean rank=28.42, median=6), than the TAP block group (mean rank= 20.58, median=5), U=194.00, z= -1.989, *p=0.047*.

Static pain 3^{-th} h

The medians of both groups show one and the same value (median=3). The mean rank of TAP block group (22.92) is lower than the mean rank of control group (26.08). No statistically significant difference is observed, U=250.00, z= -0.842, *p=0.4*.

Static pain 6^{-th} h

No statistically significant difference is observed between the groups. TAP block group (median=3, mean rank=24.67), vs control group (median=3, mean rank=24.33), U=284.00, z= -0.093, *p=0.926*.

Static pain 12-th h

The control group has a median=2.5 and the mean rank is 25.63, whereas the TAP block group has a median=2 and mean rank= 23.38. There is no statistically significant difference between the groups U=261, z= -0.607, *p=0.554.*

Static pain 24-th h

The medians of both groups are the same (median=2). The mean rank of TAP block group is 25.75, the mean rank of control group is 23.25. There is no statistically significant difference between the groups U=258, z= -0.760, *p=0.447*

Independent sample T test

Static pain 0 hour

The mean values of control group VNS are higher (5.4±1.3), compared to TAP block group values (4.6±1.3). The mean difference of 0.79±0.4 is statistically significant (95% CI -1.545— -0.376, t(46)= -2.113, *p*=0.04).

Static pain 3-th hour

The mean values of control group VNS are higher (3.3±0.7), compared to TAP block group values (3±0.9). The mean difference of 0.17±0.24 is not statistically significant (95% CI -0.653— -0.320, t(46)= -0.689, *p*=0.495).

Static pain 6-th hour

The mean values of both groups are the same, i.e. there is no difference (95% CI -0.392— 0.392, t(46)= 0, *p=1*).

Static pain12-th h

The mean values of control group VNS are higher (2.6±0.7), compared to TAP block group values (2.5±0.9). The mean difference of 0.12±0.23 is not statistically significant (95% CI -0.591— 0.341, t(46)= -0.540, *p=0.529*).

Static pain 24-th h

The mean values of VNS of TAP block group are higher (1.95±0.7), compared to the control group (1.8±1). The mean difference of 0.1±0.2 is not statistically significant (95% CI -0.185— 0.519, t(46)= 0.952, *p=0.346*).

Discussion comment

Both, TAP block and the control group, present the highest mean values of VNS immediately after the intervention. At the 3^{-th} post-operative hour, the average values of VNS significantly decreased. This trend of decreasing values persisted in both groups until the end of the first postoperative day. A statistically significant difference in the values of VNS between the groups, assessed with a parametric (fig. 20) and non-parametric test (table 11), was registered only in the immediate postoperative period (p=0.04). During the other time periods, the VNS values did not show statistically significant differences. TAP block does not clinically significantly affect postoperative static pain in patients undergoing robotic hysterectomy.

Table 11 Sum of ranks and mean ranks of values of VNS for static pain of RH groups.

	TAP block	Count	Mean rank	Sum of ranks
VNS 0h	YES	24	20.58	494.00
	NO	24	28.42	682.00
VNS 3h	YES	24	22.92	550.00
	NO	24	26.08	626.00
VNS 6h	YES	24	24.67	592.00
	NO	24	24.33	584.00
VNS 12h	YES	24	23.38	561.00
	NO	24	25.63	615.00
VNS 24h	YES	24	25.75	618.00
	NO	24	23.25	558.00

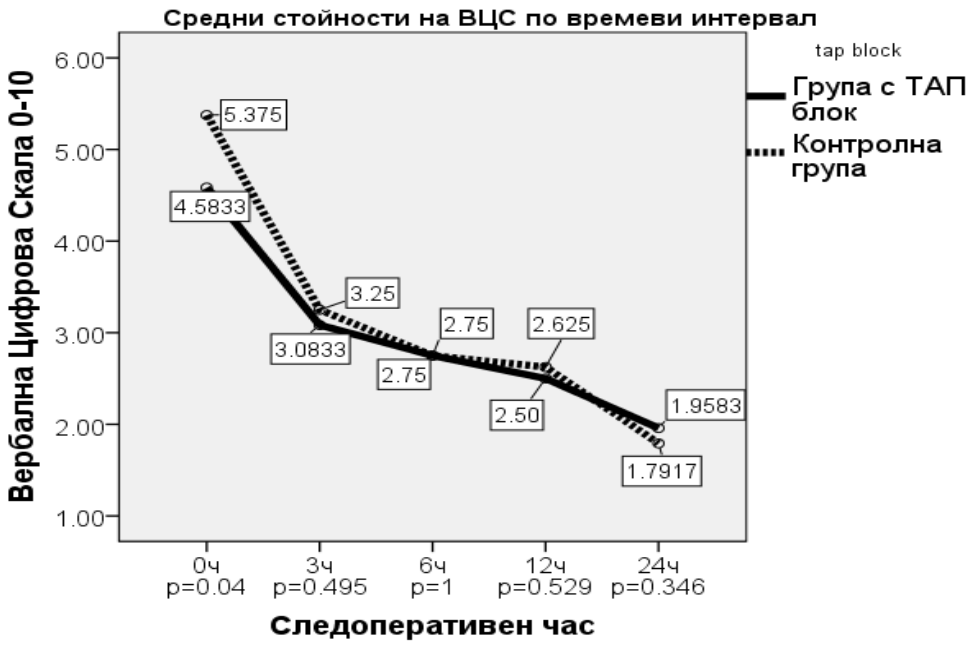


Figure 20 Means of VNS values for static pain in different time moments of RH group.

Verbal Numeric Scale for dynamic pain evaluation.

Mann-Whitney U test

Dynamic pain 0 hour

The control group presents higher values of mean rank and median (mean rank=26.44, median=6), than the TAP block group (mean rank=22.56, median=5.5). This difference is not statistically significant, U=241.500, z= -0.990, *p=0.322*.

Dynamic pain 3^{-th} hour

The median of both groups is the same (median=5). TAP block group has higher mean rank (25.21), than the control group (mean rank=23.79). This difference is not statistically significant, U=271.000, z= -0.370, *p=0.712*.

Dynamic pain 6^{-th} hour

The median of both groups is the same (median=4). Control group demonstrates higher values of mean rank(26.02), than TAP block group (mean rank=22.98). This difference is not statistically significant, U=251.500, z= -0.807, *p=0.420*.

Dynamic pain 12^{-th} hour

Control group has a mean rank(27.60) and median (4), higher than TAP block group(mean rank=21.40, median=3). The difference is not statistically significant U=213.500, z= -1.732, *p=0.083*.

Dynamic pain 24-th hour

The median of both groups is the same (median=3). Control group has higher values of mean rank (24.65), than TAP block group (mean rank=24.35). The difference is not statistically significant, U=284.500, z= -0.081, *p=0.936*.

Independent sample T test

Dynamic pain 0 hour

The mean values of control group VNS are higher (6±1.4), compared to TAP block group values (5.5±1.2). The mean difference of 0.5±0.38 is not statistically significant (95% CI -1.261— 0.261, t(46)= -1.322, *p=0.193*).

Dynamic pain 3-th hour

The mean values of VNS are higher in TAP block group (5±1.2), compared to the control one (4.9±0.8). The mean difference of 0.16±0.29 is not statistically significant (95% CI -0.424— -0.757, t(46)= 0.568, *p=0.573*).

Dynamic pain 6-th hour

The mean values of control group VNS are higher (4.4±0.7), compared to TAP block group values (4.1±0.9). The mean difference of 0.25±0.24 is not statistically significant (95% CI -0.241— -0.736, t(46)= -1.034, *p=0.306*).

Dynamic pain 12-th hour

The mean values of control group VNS are higher (3.8±0.6), compared to TAP block group values (3.5±0.6). The mean difference of 2±0.33 is not statistically significant (95% CI -0.633— 0.505, t(46)= -1.715, *p=0.093*).

Dynamic pain 24-th hour

The mean values of control group VNS are higher (7.3±1.2), compared to TAP block group values (5.2±1.4). The mean difference of 2±0.33 is not statistically significant (95% CI -0.408— -0.324, t(46)= -0.229, *p=0.820*).

Discussion comment

The subjective indicators of dynamic pain in both studied groups demonstrate their highest values in the immediate postoperative period. During the next four time intervals, the mean values of VNS decreases progressively in the both groups. The comparison with non-parametric (table 12) and parametric (fig. 21) statistic tests does not show statistically significant differences between the groups in all the time intervals.

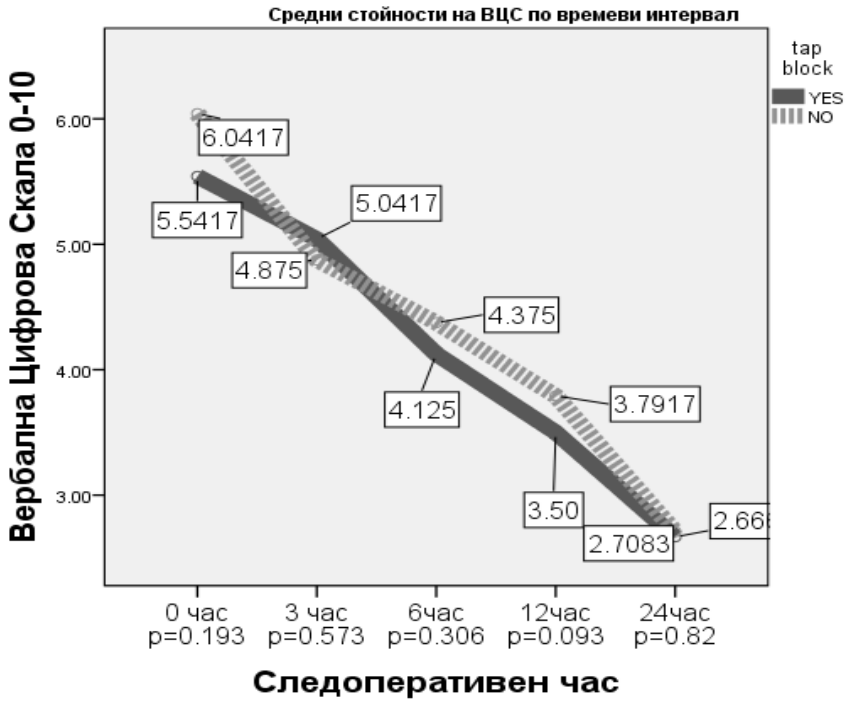


Figure 21 Means of VNS values for dynamic pain in different time moments RH group.

Table 12 Sum of ranks and mean ranks of values of VNS for dynamic pain of RH group.

	TAP block	Count	Mean rank	Sum of ranks
VNS 0h	YES	24	22.56	541.50
	NO	24	26.44	634.50
	Total	48		
VNS 3h	YES	24	25.21	605.00
	NO	24	23.79	571.00
	Total	48		
VNS 6h	YES	24	22.98	551.50
	NO	24	26.02	624.50
	Total	48		
VNS 12h	YES	24	21.40	513.50
	NO	24	27.60	662.50
	Total	48		
VNS 24h	YES	24	24.35	584.50
	NO	24	24.65	591.50
	Total	48		

Incidence of nausea and vomiting

In both studied groups, no symptoms of severe nausea and vomiting were observed. TAP block group and the control group have the majority of patients who do not have any signs of nausea and vomiting (n=20 in the TAP block group and n=16 in the control group). The patients who showed a mild degree of nausea were, respectively, n=3 in the TAP block group and n=6 in the control group. Moderate nausea occurred in only one patient in the TAP block group (n=1) and in two patients in the control group (n=2). No patient had severe nausea with vomiting (n=0), (table13). The two groups demonstrate the same median values (median=1 for TAP block group and control group). The rank sums have higher values in the control group (mean rank=26.50, sum of ranks=636), compared to the TAP block group (mean rank=22.50, sum of ranks=540). This difference is not statistically significant U=240, z= -1.309, p=0.190.

Table 13 Count and number of nauseas and vomiting like an opioid side effect of RH group.

		TAP block		
		YES	NO	TOTAL
No symptoms	Count	20	16	36
	% in Group	83.3%	66.7%	75.0%
Mild nauseas	Count	3	6	9
	% in Group	12.5%	25.0%	18.8%
Moderate nauseas	Count	1	2	3
	% in Group	4.2%	8.3%	6.3%
TOTAL	Count	24	24	48
	% in Group	100.0%	100.0%	100.0%

Ramsay sedation score

Ramsay0 hour

At the admission to ICU, patients with Ramsay sedation score 3 predominates in both groups (n=14, 58.3% for the TAP block group and n=15, 62.5% for the control group). The number of patients with Ramsay sedation score 2 is higher in the TAP block group (n=9, 37.5%) compared to the control group (n=8, 33.3%). In both groups, Ramsay sedation score 1 is registered to only one patient (n=1, 4.2% for both groups). The difference between the groups is not statistically significant, p=0.552 (Fisher's exact test 2xR).

Ramsay3^{-th} hour

In both groups, patients with Ramsay sedation score 2 predominate (n=18, 75% for the TAP block group and n=16, 66.7%, for the control group). The number of patients with Ramsay sedation score 3 is higher in the control group (n=7, 29.2%) compared to the TAP block group (n=6, 25%). In the control group, there is only one patient with Ramsay sedation score 1 (n=1, 4.2% of the group). The difference between the groups is not statistically significant p=0.954 (Fisher's exact test 2xR).

Ramsay6^{-th} hour

In both groups, patients with Ramsay sedation score 2 predominate (n=19, 79.2% for the TAP block group and n=20, 83.3%, for the control group). The number of patients with Ramsay sedation score 3 is higher in the TAP block group (n=5, 20.8%), compared to control group (n=4, 16.7%), (table31). The difference between the groups is not statistically significant *p=0.312* (Fisher's exact test 2xR).

Ramsay12^{-th} hour

In both groups, patients with Ramsay sedation score 2 predominate (n=23, 95.8% for the TAP block group, n=24, 100% for the control group). The difference between the groups is not statistically significant *p=0.64* (Fisher's exact test 2xR).

Ramsay24^{-th} hour

On the 24-th postoperative hour all the patients, in both groups, have Ramsay sedation score 2 (n=24, 100% for the TAP block group, n=24, 100% for the control group).

Discussion comment

The two groups do not show any statistically significant differences in the level of consciousness assessed by the Ramsay sedation score scale. The TAP block did not demonstrate clinical effectiveness on the level of consciousness in patients undergoing robotic hysterectomy.

Pruritus

In the control group 2 patients reported this complication (n=2, 8.3%), where as in the TAP block group 3 (n=3, 12.5%). The difference is not statistically significant (p=0.707 Fisher's exact test 2xR).

Statistical analysis of the patients with laparoscopic hysterectomy

Study design

Fifty-five women with LH were assessed for eligibility in the trial and all of them were enrolled in the study. For different reasons 9 patients dropped out. Overall, 46 patients completed the study and were analyzed (fig.22).

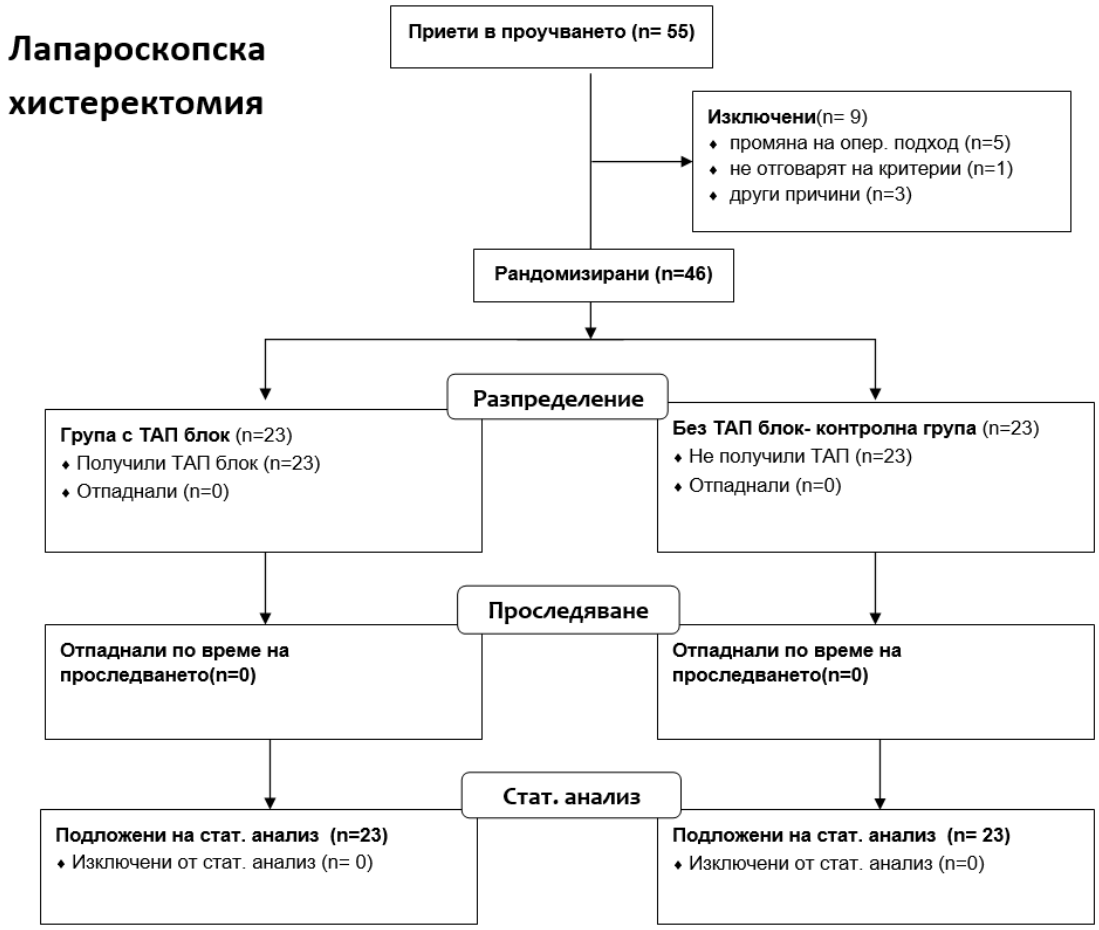


Figure 22 CONSORT diagram of study design of LH group

Patients' demographic characteristics

No statistically significant differences were observed between the two groups in terms of age, weight, height, BMI, ASA grade and the time of surgery (table14).

Table 14 Patients' demographic characteristics of LH group.

Group	**TAP block group**	**Control group**	***P significance***
Age(years)	57.6±5.2	55.6±2.5	*p*=0.115
BMI	25.6±3.5	24.2±1.9	*p*=0.113
Operative time (min)	149±5 min	150±4	*p*=0.425
ASA			*p=0.236*

Fentanyl consumption during surgery

The mean intraoperative consumption of fentanyl was higher in the control group (167µg±14µg), than in the TAP block group (160µg ±15 µg) (fig.23). The difference is not statistically significant U=187.500, z= -1.915, *p=0.055*Mann-Whitney U test (table15).

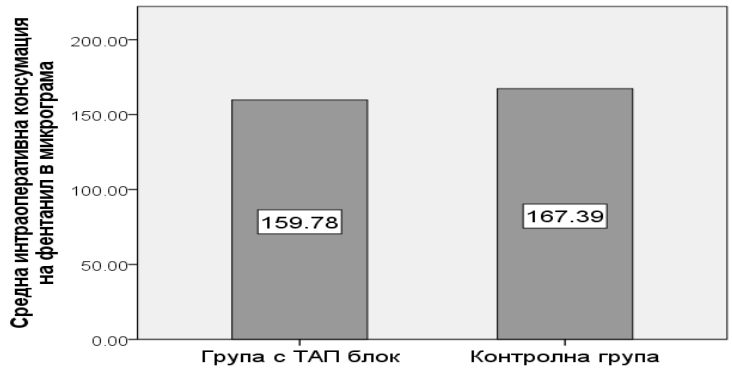


Figure 23 Mean Fentanyl consumption in µg of LH group.

Table 15 Mean ranks and sum of ranks of the values of intraoperative consumption of Fentanyl of LH group

	TAP block	N	Mean rank	Sum of ranks
	YES	23	20.15	463.50
	NO	23	26.85	617.50
	Total	46		

Morphine consumption

Morphine loading dose

The mean amount of morphine, used for loading dose in ICU was higher in TAP block group (3.22±0.8mg), than in the control group, (3.26±0.7mg) (fig.24). The normality of data distribution is violated, so Mann-Whitney U test is conducted. The medians of the groups have the same value (median=3). Mean rank and rank sum are higher in the control group (table16). The difference presents no statistical significance, U=258.500, z= -0.154, *p=0.878.*

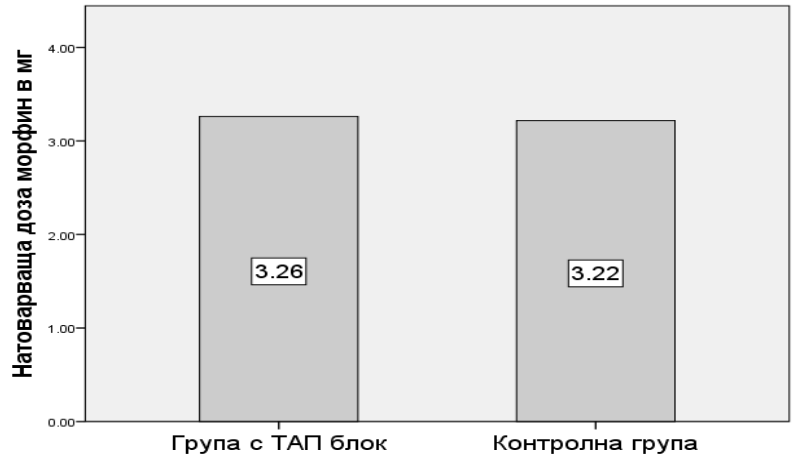


Figure 24 Mean loading dose of Morphine of LH group.

Table 16 Mean ranks and sum of ranks of the loading Morphine dose of LH group

	TAP block	N	Mean rank	Sum of ranks
	YES	23	23.78	547.00
	NO	23	23.22	534.00
	Total	46		

Morphine consumption for the first 12 postoperative hours

The mean cumulative consumption of morphine for the first 12 postoperative hours was higher in the control group (8.3±1.45mg), than in the TAP block group (7.9±1.6mg), (fig.25). The mean difference of 0.4±0.4mg has no statistical significance (95% CI -1.337— 0.467, t(44)= -0.971, *p*=0.337).

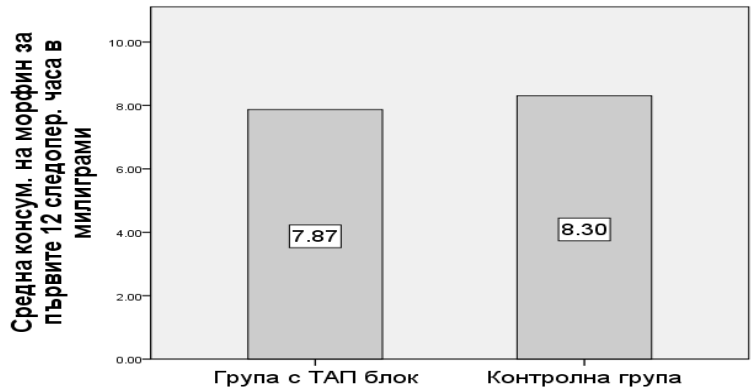


Figure 25 Mean Morphine consumption in mg for 0-12-th postoperative hour LH group.

Morphine consumption for the second 12 postoperative hours

The mean cumulative consumption of morphine for the second 12 postoperative hours was higher in the TAP block group (4.3±1mg), than the control group (4±1mg), (fig.26). The difference of 0.3±0.3mg has no statistical significance. (95% CI -0.325— 0.934, t(44)= 0.974, *p=0.335*).

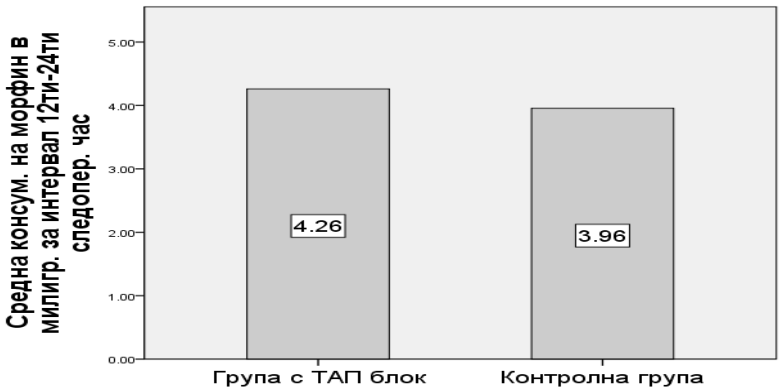


Figure 26 Mean Morphine consumption in mg 12-th -24-th postoperative hour LH group

Cumulative 24 hours Morphine consumption

The mean cumulative consumption of morphine for the first 24 postoperative hours was higher in the control group, (15.5±2mg), than in the TAP block group (15.4±2mg), (fig.27). The mean difference of 0.08±0.6mg is not of statistical significance, (95% CI -1.395— 1.221, t(44)= -0.134, *p=0.894*).

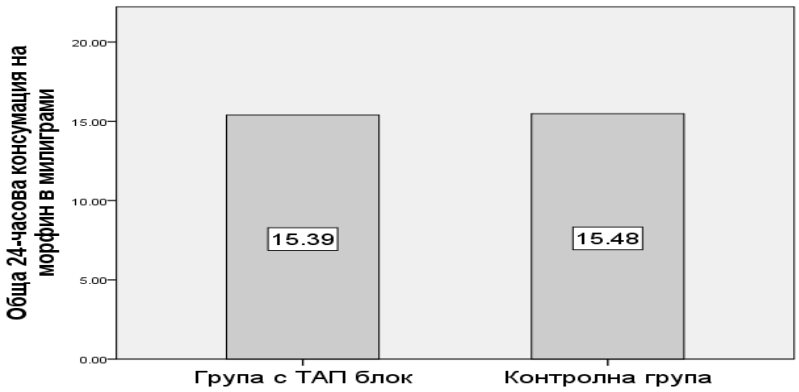


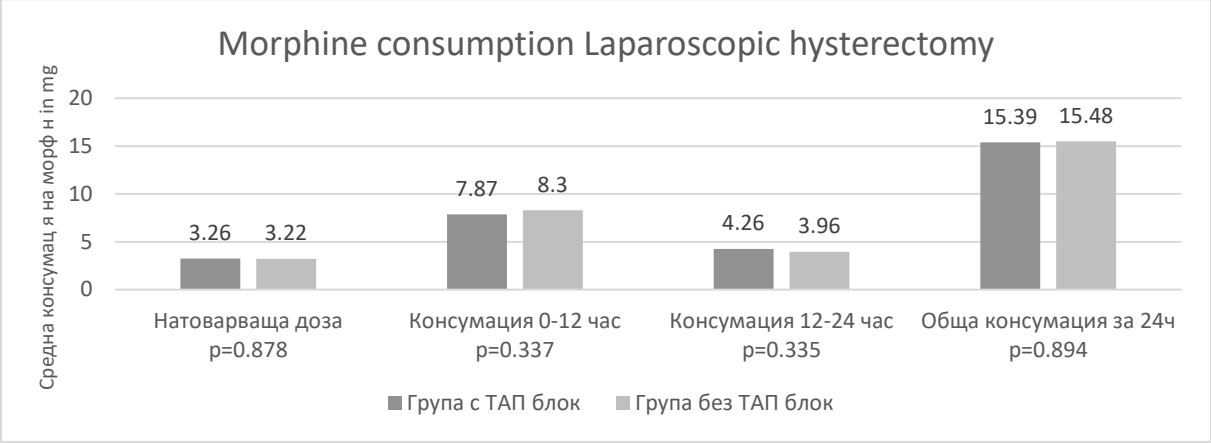
Figure 27 Mean total 24 hours consumption of Morphine LH group

Discussion about Morphine consumption

At the 12th postoperative hour, the TAP block group consumed less Morphine than the control group, but without any statistical significance (p=0.337). During the second 12 postoperative hours, an inversion of the result is observed - the control group consumed less

opiate than the group with an applied local blockade. The difference presents no statistical significance (p=0.335). The average total 24-hour morphine consumption was lower in the TAP block group, but without statistical significance (p=0.894), (table17).

Table 17



Verbal Numeric Scale for static pain evaluation.

Mann-Whitney U test

Static pain 0 hour

The medians of both groups show one and the same value (median=5). TAP block group mean rank (26.48) is higher than control group (mean rank=20.52). No statistically significant difference is observed U=196.000, z= -1.641, *p=0.101*.

Static pain 3^{-th} hour

Control group demonstrates higher values of mean rank (26.28) and median (4), whereas the TAP block group has a mean rank=20.72 and median=4. There is no statistically significant difference between the groups U=200.5, z=-1.521, *p=0.128*.

Static pain 6^{-th} hour

TAP block group has a median (5), higher than control group (median=4). The mean mean rank (26.78) and sum of ranks (616) are higher in TAP block group, than the control one (mean rank= 20.22 sum of ranks =465). There is no statistically significant difference between the groups U=189.000, z=-1.757, *p=0.079*.

Static pain 12^{-th} hour

TAP block group demonstrates a higher median (median=4), than control group (median=3). The mean rank and sum of ranks of TAP block group (mean rank=27.07, sum of ranks=622.5), are higher than control group(mean rank=19.93, sum of ranks=458.5). There is no statistically significant difference between the groups U=182.500, z= -1.937, *p=0.053*.

Static pain 24-th hour

The median of both groups is the same (median=2). The mean rank and sum of ranks TAP block group (mean rank=25.89, sum of ranks=595.5), are higher than control group(mean rank=21.11, sum of ranks=485.5). The differences are not statistically significant. U=209.500, z= -1.354, *p=0.176*.

Independent sample T test

Static pain 0 hour

The mean values of TAP block group VNS are higher (5.2±0.6), than the values of the control group(4.9±1). The mean difference of 0.3±0.3 is not statistically significant (95% CI -0.176— 0.872, t(44)= 1.337, *p=0.188*).

Static pain 3-th hour

The mean values of control group VNS are higher (4.4±0.7), compared to TAP block group values (4.9±1). The mean difference of 0.5±0.3 is not statistically significant (95% CI -1.06896— 0.025, t(44)= -1.922, *p=0.061*).

Static pain 6-th hour

The mean values of TAP block group VNS are higher (4.5±0.6), than the values of the control group (4.2±1.2). The mean difference of 0.3±0.3 is not statistically significant (95% CI -0.276— 0.884, t(31.701)= 1.069, *p=0.293*).

Static pain 12-th hour

The mean values of TAP block group VNS are higher (3.8±0.9), than the values of the control group (3.3±0.6). The mean difference of 0.4±0.23 is not statistically significant (95% CI -0.031— 0.901, t(44)= 1.878, *p=0.067*).

Static pain 24-th hour

The mean values of TAP block group VNS are higher (2.2±0.7), than the values of the control group (1.9±0.6). The mean difference of 0.3±0.2 is not statistically significant (95% CI -0.128— 0.650, t(44)= 1.351, *p=0.184*).

Discussion comment

Both in the TAP block group and in the control group, the highest average values of VNS for static pain were reported in the initial postoperative period. The pain values are higher in the TAP block group. During the next four periods, the average values of VNS decreases progressively. This trend applies to both studied groups. At the 6th, 12th, and 24th postoperative hour, the control group demonstrated lower average pain scores than the TAP block group.

There were no statistically significant differences between the two groups, evaluated with parametric (fig.28) and non-parametric tests (table18).

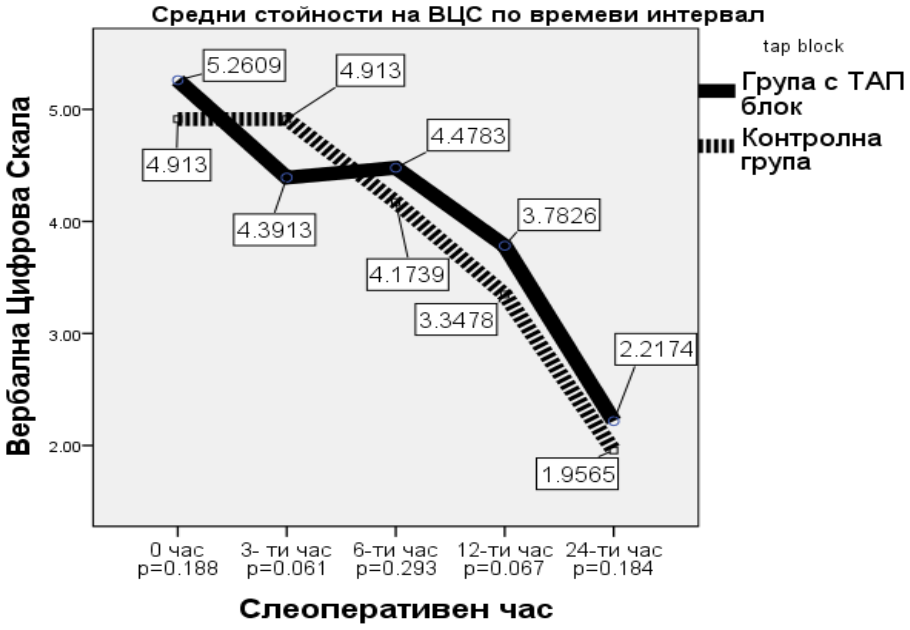


Figure 28 Means of VNS values for static pain in different time moments of LH group.

Table 18 Sum of ranks and mean ranks of values of VNS for static pain of LH group.

	TAP block	Count	Mean rank	Sum of ranks
VNS 0h	YES	23	26.48	609.00
	NO	23	20.52	472.00
VNS 3h	YES	23	20.72	476.50
	NO	23	26.28	604.50
VNS 6h	YES	23	26.78	616.00
	NO	23	20.22	465.00
VNS 12h	YES	23	27.07	622.50
	NO	23	19.93	458.50
VNS 24h	YES	23	25.89	595.50
	NO	23	21.11	485.50

Verbal Numeric Scale for dynamic pain evaluation.

Mann-Whitney U test

Dynamic pain 0 hour

The control group and TAP block group have the same median (median=6). The mean rank and sum of ranks are higher in the control group (mean rank=26.89, sum of ranks=618.50), than TAP block group (mean rank= 20.11, sum of ranks=462.50). There is no statistically significant difference between the groups U=186.5, z= -1.827, *p=0.068*.

Dynamic pain 3-th hour

The median of TAP block group (median=6) is higher than the median of control group (median=5). The mean rank and sum of ranks of TAP block group (mean rank=25.63, sum of ranks=589.5) are higher than control group (mean rank=21.37, sum of ranks=491.5). The differences are not of statistical significance. U=215.5, z= -1.129, *p=0.259*

Dynamic pain 6-th hour

The medians of both groups are the same (median=5) Control group demonstrates higher mean rank and sum of ranks (mean rank=25.13, sum of ranks=578), than TAP block group (mean rank=21.87, sum of ranks=503). No statistically significant difference is observed, U=277, z= -0.855, *p=0.393*.

Dynamic pain 12-th hour

The medians of both groups are the same (median=4). The mean rank and sum of ranks are lower in control group (mean rank=22.87, sum of ranks=526), than TAP block group (mean rank= 24.13, sum of ranks=555). There is no statistically significant difference between the groups U=250.000, z= -0.331, *p=0.741*.

Dynamic pain 24-th hour

Control group and TAP block group has equal medians (median=4). The mean rank and sum of ranks are higher in the control group (mean rank=26.35, sum of ranks=606), than TAP block group (mean rank=20.65, sum of ranks=475). There is no statistically significant difference between the groups U=199.000, z= -1.650, *p=0.099*.

Independent sample T test

Dynamic pain 0 hour

The mean values of control group VNS are higher (6.1±1), compared to TAP block group values (5.7±0.8). The mean difference of 0.4±0.3 is not statistically significant (95% CI -0.968— 0.988, t(44)= -1.642, *p=0.108*).

Dynamic pain 3-th hour

The mean values of TAP block group VNS are higher (6±0.8), compared to the control group (5.7±1). The mean difference of 0.3±0.3 is not statistically significant (95% CI -0.273— 0.882, t(40.858)= 1.064, *p=0.294*).

Dynamic pain 6-th hour

The mean values of control group VNS are higher (5.3±1), compared to TAP block group values (4.8±1.5). The mean difference of 0.4±0.4 is not statistically significant (95% CI -1.224— 0.355, t(44)= -1.109, *p=0.273*).

Dynamic pain 12-th hour

The mean values of TAP block group VNS are higher (4.3±1.4), compared to the control group (4.2±0.7). The mean difference of 0.1±0.3 is not statistically significant (95% CI -0.546— 0.807, t(34.456)= .391, *p=0.698*).

Dynamic pain 24-th hour

The mean values of control group VNS are higher (3.9±0.5), compared to TAP block group values (3.6±0.9). The mean difference of 0.3±0.2 is not statistically significant (95% CI -0.749— 0.140, t(32.641)= -1.392, *p=0.173*).

Discussion comment

The control group progressively reduces the average values of VNS in the postoperative period from the beginning to the end of the first day. TAP block group increases the average values of VNS at the 3-th postoperative hour. This is followed by a progressive decrease in the pain score over the next three time periods. At the admission to ICU, at the 6th and 24th hour, the subjective pain index for dynamic pain presents higher values in the control group compared to the TAP block group. At the 3th and 12th hours, an inversion of the results was found (the TAP block group demonstrated higher values of VNS). The established differences between the groups have no statistical significance in any of the time intervals (fig. 29 and table 19).

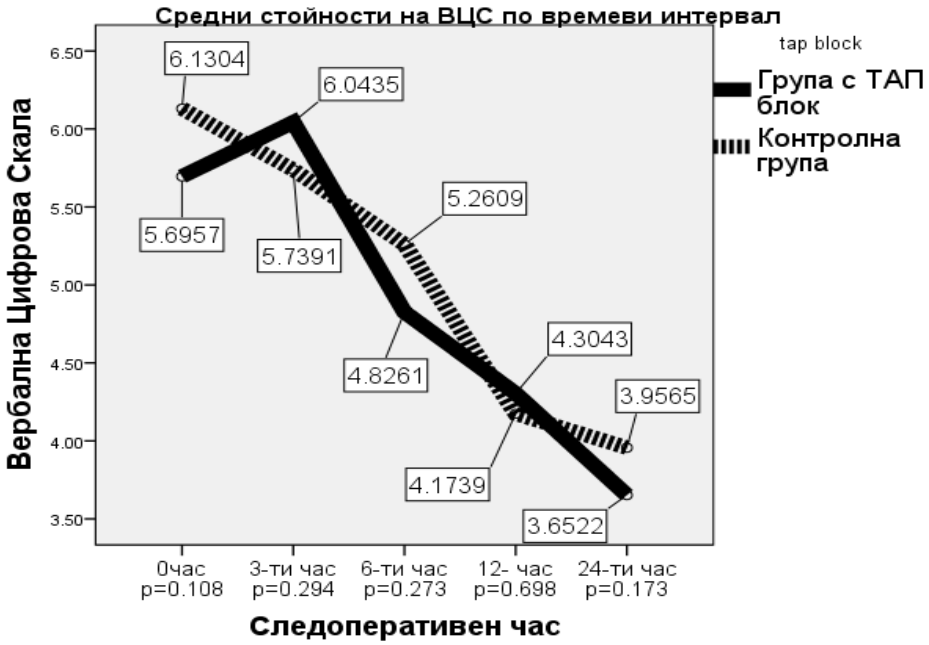


Figure 29 Means of VNS values for dynamic pain in different time moments of LH group.

Table 19 Sum of ranks and mean ranks of values of VNS for static pain of LH groups

	TAP block	Count	Mean rank	Sum of ranks
VNS 0h	YES	23	20.11	462.50
	NO	23	26.89	618.50
	Total	46		
VNS 3h	YES	23	25.63	589.50
	NO	23	21.37	491.50
	Total	46		
VNS 6h	YES	23	21.87	503.00
	NO	23	25.13	578.00
	Total	46		
VNS 12h	YES	23	24.13	555.00
	NO	23	22.87	526.00
	Total	46		
VNS 24h	YES	23	20.65	475.00
	NO	23	26.35	606.00
	Total	46		

Incidence of nausea and vomiting

In both groups, the majority of patients do not present any symptoms of nausea and vomiting (n=19 or 82.6% in the TAP block group and n=16 or 69.6% in the control group). The patients who had a mild degree of nausea were respectively n=2 (8.7%) in the TAP block group and n=5 (21.7%) in the control group. Moderate nausea occurred in only one patient in TAP block group (n=1, 4.3%) and in two patients in the control group (n=2, 8.7%). Severe nausea with vomiting was registered in only one patient in the TAP block group (n=1, 4.3%), while in the control group there was not such a case(n=0), (table20). The two groups have the same median (median=1 for TAP block group and control group). The sum of ranks are higher in the control group (mean rank=24.83, sum of ranks=571), compared to the TAP block group (mean rank=22.17, sum of ranks=571). This difference is not statistically significant, U=234.000, z= -0.899, p=0.369.

Table 20 Incidence of nauseas and vomiting in LH group.

		TAP block		
		YES	NO	TOTAL
No symptoms	Count	19	16	35
	% in Group	82.6%	69.6%	76.1%
Mild nauseas	Count	2	5	7
	% in Group	8.7%	21.7%	15.2%
Moderate nauseas	Count	1	2	3
	% in Group	4.3%	8.7%	6.5%
Severe nauseas and vomiting	Count	1	0	1
	% in Group	4.3%	.0%	2.2%
TOTAL	Count	23	23	46
	% in Group	100.0%	100.0%	100.0%

Ramsay sedation score

Ramsay0 hour

At the admission to ICU, patients with Ramsay sedation score 3 predominates in both groups (n=16, 69.6% for the TAP block group n=17, 73.9%, for the control group). The difference between the groups is not statistically significant $\chi^2(1)=0.107$, *p=0.743*.

Ramsay3^{-th} hour

In both groups, patients with Ramsay sedation score 2 predominate (n=19, 82.6% for the TAP block group, n=18, 78.3% for the control group). The difference between the groups is not statistically significant, Fisher's exact test 2xR *p=0.51*.

Ramsay6^{-th} hour

In TAP block group all the patients have Ramsay sedation score 2(n=23, 100%)**.** In the control group only one patient has Ramsay sedation score 3 (n=1, 4.3%) The difference between the groups is not statistically significant, Fisher's exact test 2xR *p=0.88*.

Ramsay12^{-th} hour

On the 12th postoperative hour in both groups predominate the patients with Ramsay sedation score2 (n=22, 95.7% for the TAP block group, n=22, 95.7% for the control group), (table47). The difference between the groups is not statistically significant (Fisher's exact test 2xR *p=1*).

Ramsay24^{-th} hour

All the patients of TAP block group and the control group have Ramsay sedation score2 (n=23, 100% for the TAP block group, n=23, 100% for the control group)

Discussion comment

The two studied groups did not show statistically significant differences in the level of consciousness assessed by the Ramsay scale in any of the five time intervals. The TAP block did not demonstrate clinical effectiveness on the level of consciousness in patients undergoing laparoscopic hysterectomy.

Pruritus

In the control group 3 patients reported this complication (n=3, 13%), where as in the TAP block group there were only 2 (n=2, 8.7%). The difference is not statistically significant (p=1 Fisher's exact test 2xR).

V. Discussion

During our study, that lasted about five years, a significant number of ultrasound-guided TAP blocks was performed. We did not register any complications on account of TAP block. No clinical manifestations of local anesthetics systemic toxicity were recorded. Unfortunately, we did not have the opportunity to examine the plasma concentration level of Ropivacaine. This could be a subject of future studies.

We fulfilled our main objective. We evaluated the analgesic effect after application of TAP block in three types of hysterectomy. Our working hypothesis was confirmed only in the groups with abdominal and robotic approach of hysterectomy, where TAP block led to a statistically significant reduction in mean 24-hour postoperative morphine consumption.

We found that intraoperative Fentanyl consumption was reduced to a statistically significant level the TAP group with abdominal hysterectomy. No clinically significant difference was found in the robotic and laparoscopic techniques. This could be due to the specificity of microinvasive surgery technics. The TAP block demonstrated no potential to counteract the pain, on the count of the diffuse anterolateral abdominal wall distension and pleural effusion due to gas-increased intra-abdominal pressure.

We proved that TAP block ameliorates the subjective feeling of pain, assessed by International Verbal Numerical Scale. This phenomena is observed only in the patients undergone abdominal hysterectomy via Pfannenstiel incision and concerns both static and dynamic pain. In laparoscopic and robotic operative techniques, the results were opposite. No statistical significance was observed.

The opioid complication analysis as nausea and vomiting, impaired consciousness, pruritus demonstrated that the TAP block did not clinically affect their frequency. No statistically significant differences between the groups were observed for all three studied types of hysterectomy.

Our experience, expressed in the present work, shows that the TAP block offers sufficient analgesia potential for interventions with anterior-lateral abdominal wall approach in operative gynecology. We reported that this analgesic effect was most pronounced in abdominal hysterectomy. We confirmed the study results of other authors that TAP block does not affect visceral pain, only somatic one. Our work confirms the lack of a clinically relevant neuroprotective effect of this locoregional blockade.

We propose that the technique of TAP block under ultrasound guidance schould be included in analgesia protocols for abdominal hysterectomy with Pfannenstiel incision. TAP block is also suitable for analgesia during caesarean section, myomectomy, cystectomy,

herniotomy, appendectomy, abdominoplasty and other operations associated with minimal visceral pain.

Limitations of the study

1. No placebo group was formed, because of medico-ethical considerations.
2. The study is not blind.
3. The interventions were performed by different operators.
4. There is no hourly calculation of Morphine use. Only on 12^{-th} and 24^{-th} hour
5. Neuroprotective effect of TAP block was evaluated only in AH group.

VI. Conclusions

1. TAP block leads to a decrease of total 24 hours postoperative Morphine consumption after abdominal, laparoscopic and robot-assisted hysterectomy. This effect is most significant in the abdominal hysterectomy group.
2. TAP block decreases intraoperative Fentanyl consumption.
3. The peripheral nerve block in TAP has no significant effect on perioperative opioid consumption when robotic or laparoscopic approach for hysterectomy is used.
4. TAP block leads to a clinically significant amelioration of the subjective feeling for static pain for hysterectomy via Pfannenstiel. TAP block does not affect the subjective feeling of static pain when laparoscopic or robotic approach for hysterectomy is used.
5. TAP block leads to a clinically significant amelioration of the subjective feeling for dynamic pain for hysterectomy via Pfannenstiel. TAP block does not affect the subjective feeling of dynamic pain when laparoscopic or robotic approach for hysterectomy is used.
6. TAP block does not affect the incidence of pruritus as an opioid-side effect.
7. TAP block does not affect the incidence of opioid-side effects nausea and vomiting.
8. TAP block does not affect the level of consciousness like opioid-side effect.
9. TAP block does not possess a significant neuroprotective potential.
10. The ultrasound control when performing TAP block turs it in a safe, reliable, and sure loco regional technic of analgesia.

VII. Contributions

Scientific and theoretical contributions

1. For the first time in Bulgaria is explored the effect of a TAP block, under US control, with Ropivacaine for gynecological interventions.
2. For the first time in Bulgaria an evaluation of Ropivacaine potential for "preventive analgesia" when applied in TAP is realized.
3. A diagram about contemporary opioid-sparing medical opportunities in postoperative pain relief after hysterectomy is prepared.
4. An author's photo with a schematic representation of the external landmarks used to identify Petit's triangle is proposed.
5. A figure with detailed description of sonographic stages of the TAP block is created.
6. An author's photo with a schematic presentation of pre-marked external body anatomical landmarks and the position of the ultrasound probe, when performing a TAP block with lateral access was created.

Affirmative Contributions

1. For the first time in Bulgaria, we confirm the TAP block potential to improve peri-operative analgesia during gynecological interventions related to removal of the uterus. We used only morphine for postoperative analgesia. Our goal was to evaluate the pure effectiveness of this locoregional analgesia technique. The obtained results are comparable to the results from previous studies in the same scientific field.
2. For the first time in Bulgaria, we confirm the perioperative, opioid-sparing effect of the TAP block for ablation of uterus with different surgical approach.
3. For the first time in Bulgaria, we confirm the beneficial effect of the TAP block on the pain feeling after hysterectomy. The clinical significance of this is the increased patient comfort.

Scientific and practical contributions

1. Based on our experience in practice of TAP block, we could recommend its acquisition as one of the initial techniques when training anesthesiologists with ultrasound usage.
2. The created analgesia and psycho-neurological comfort for the patient when applying a TAP block, proposes a real clinical application.

VIII. Application

Publications related to the dissertation work:

1. Penev G., Grigorov E. Analgesic efficacy of preoperative ultrasound transversal abdominal plane block for open hysterectomy. Biotechnol Biotechnol Equip. 2022 May 31;36(1):346–52. DOI: 10.1080/13102818.2022.2081515 **[Impact factor 1.632]**
2. Penev G. Analgesic effect of Transversal Abdominal Plane block in patients with abdominal hysterectomy via Pfannenstiel approach. Obstetrics & Gynecology. 2020;59(4):45–51.
3. Penev G., Grigorov E., Georgiev S. Contemporary principles and classification of peripheral nerve blocks. Medical review. 2022;58(1):11–20.

Qualifications and skill trainings:

1. Online training education „Lung Protective Ventilation in the Operating Room“, GE Healthcare, 10.V.2022
2. Participation on Seventh Pharmaceutical Business Forum with Scientific and Practical Conference “Digital solutions and innovation in pharmaceutical practice and education - challenges and opportunities” ONLINE on 22-23 October 2021, Medical University of Varna, Bulgaria, *Scripta Scientifica Pharmaceutica (ISSN 2367-5500),* 2021, Vol. 8, No. 1, Suppl. 1, p.41. NEUROAXIAL APPLICATION OF MORPHINE.
3. Post graduate diplome „Flexible fiber-optic bronchoscopy level 1“. Certificate:ПК № 4282/30.01.2019.
4. Participation on scientific medical congress „Journées Lilloises d’Anesthesie Réanimation et Médecine d’Urgence ARCL Lille”, 2012, France.
5. Acquired diplome for university assistant „ Ancien Chef de clinique des universités-assistant des hôpitaux” after 2 years training course at Centre Hospitalier Régionale Universitaire de Lille. Certificate Réf: GR/SR 28.01.2013.