Research Article

Argonoperitoneum Effect on Pain Syndrome Intensity in Laparoscopic Cholecystectomy

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Abstract

The objective of the research was to compare the objective and subjective indicators of intra- and postoperative pain and surgical stress intensity.

Materials and Methods. There were examined 360 patients suffering from gallstone disease. There were used the intraoperative monitoring of nociception index by means of Analgesia Nociception Index- monitor, the determination of serum cortisol concentration, the assessment of pain syndrome in the postoperative period by means of the Numerical Rating Scale in accordance with life quality assessment and the number of injections at the patient's request.

Results. The analysis conducted indicated the reduction in pain irritation, low indices of pain syndrome and postoperative stress intensity under the effect of argonoperitoneum. Considerable reduction in the need for analgesics in the study groups served as evidence to this predicted pattern. The assumption that the noticed phenomenon can be explained by the absence of acid irritation of the peritoneum due to argon chemical neutrality being distinct from carbon dioxide was substantiated.

Conclusions. The results proved the effectiveness of argonoperitoneum application in laparoscopic surgeries.

Keywords

laparoscopic operations; pneumoperitoneum; pain syndrome.

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Problem statement and analysis of the latest research

Refinement of the operative technique of laparoscopic surgeries is aimed at performing safe and effective operation with minimal duration of in-patient treatment. In recent years, a whole set of measures aimed at achieving this goal called ERAS (Enhanced Recovery After Surgery) strategy has been developed. Along with other measures, the mentioned above strategy provides technological modifications with the aim to minimize the surgical access injury. Pneumoperitoneum is an essential and indispensable element of laparoscopic technique. In the beginning of laparoscopy imple-

mentation, special investigations on the use of alternative gases for pneumoperitoneum creation were conducted [8]. One of the studied options was the application of argon as an alternative to carbon dioxide. The advantage of this gas is its inertness and, thus, the absence of any effect on biological tissues and metabolism. The reason for its limited use was the conclusion on the increased risk of gas embolism in case of argon introduction into a vein with the Veress needle in iatrogenic venipuncture. Argon solubility in blood was found to be much lower than that of carbon dioxide, thus, direct introduction of argon into the vascular circulation may be unsafe [8].

However, the application of the Veress needle for pneumoperitoneum creation is not uncontested. Recently, most specialists have used the direct insertion of the first trocar into the abdominal cavity [3]. Therefore, the main risk factor of argonperitoneum application can be eliminated by exclusion of the Veress needle as a means of primary laparocentesis. At the same time, argonperitoneum benefits observed in individual studies have to be further investigated [3, 8].

The objective of the research was to compare the effect of argonperitoneum and carboxyperitoneum upon the intensity of intraoperative nociception, surgical stress, as well as pain syndrome assessment in the postoperative period.

1. Materials and Methods

The study included 300 patients with uncomplicated gallstone disease and 60 patients suffering from cholelithiasis and acute cholecystitis.

There were used the intraoperative monitoring of nociception index by means of Analgesia Nociception Index (ANI) -monitor [4, 5], the determination of peripheral serum cortisol concentration, the assessment of pain syndrome in the postoperative period by means of the Numerical Rating Scale (NRS) [1, 2, 6] in accordance with life quality assessment (the 36-Item Short Form Health Survey) [1, 2, 7] and the number of injections of a standardized dose of analgesic (Dexketoprofen).

All the patients underwent surgery on the day of hospitalization or were admitted to the hospital the day before surgery. Laparoscopic cholecystectomy was performed under combined general anesthesia with artificial lung ventilation. Anesthesia depth was monitored by means of the Bispectral Index (BIS) -monitor within the range of 40-60. The laparoscopic cholecystectomy technique was standardized. Direct trocar insertion was applied. Three additional trocar punctures were used for insertion of instruments. Gallbladder anatomic structures were dissected with a monopolar hook; the gallbladder duct and artery were clipped with titanium staples. The gallbladder was removed from the abdominal cavity through an extended trocar puncture

in the right subcostal area without a container. The drainage by means of a polymerized vinyl chloride (PVC) tube 4 mm in diameter was used only in the patients with acute cholecystitis. The drainage was not used in the patients with uncomplicated cholelithiasis.

In case of the necessity of changes in the surgical plan, as well as intraoperative complications (gallbladder perforation, hemorrhage, simultaneous operations), the patients were excluded from the study.

Post-operative pain management was performed at the patient's request by means of intravenous injections of Dexketoprofen at a dose of 50 mg.

The patients were divided into 4 groups: Group 1 uncomplicated gallstone disease, carboxyperitoneum; Group 1a comprised 30 patients with acute cholecystitis, carboxyperitoneum; Group 2 included 98 patients with uncomplicated gallstone disease, argonperitoneum; Group 2a comprised 30 patients with acute cholecystitis, argonperitoneum. Randomization of patient groups was conducted in accordance with the order of hospitalization. To ensure proportional age and gender group contingent, target adjustment was carried out.

The intraoperative ANI was monitored and recorded every 10 minutes. To evaluate serum cortisol concentration, blood sampling was conducted 4 times: before the operation, at the end of surgery before gas desufflation from the abdominal cavity, after restoration of unassisted breathing and the patient's awakening, and 1 hour after surgery. The subjective pain assessment and the Life Quality Index (LQI) were evaluated by interviewing the patients 1 hour, 6 hours, and 24 hours after surgery.

2. Results and Discussion

For the comparative analysis of the severity of pain syndrome during laparoscopies with different types of pneumoperitoneum, the monitoring of parasympathetic tonus together with the nociception index and analgesia evaluation with the help of the ANI-monitor (Metro Doloris, France) was performed. The method is based on the study of heart rate variability and respiratory arrhythmia. The patients'

Table 1. Dynamics of changes in the ANI at the stages of surgical interventions in patients of experimental groups.

Examination stage	ANI, % (M±m)			
	Group 1 (n=25)	Group 1a (n=25)	Group 2 (n=25)	Group 2a (n=25)
Before surgery	33.20±1.32	31.10±1.12	37.30±1.16	36.53±1.56
After pneumoperitoneum formation	75.56±1.89	69.43±0.39	79.93±1.48	74.46±2.59
Main stage of surgery	46.30±1.56	36.21±1.23	63.10±2.75	64.96±1.54
After gas desufflation	54.33±1.18	49.13±1.23	59.36±1.78	61.06±1.55

ANI was determined every 5 minutes: before gas insufflation into the abdominal cavity, at the beginning of the operation, at the main stage of surgery and after desufflation.

To counter-balance analgesia effect on ANI-monitoring results, general anesthesia depth was kept in check by means of the BIS, which was maintained in the range of 40-60.

The interpretation of the ANI in patients under general anesthesia is carried out using the following calculation:

- 0-30% – severe pain;
- 31-50% – moderate pain;
- 51-70% – adequate pain relief;
- 71-100% – opiate overdose.

In accordance with the study results of the control and experimental groups, the duration of surgery constituted 28.5 ± 8.4 min in uncomplicated gallstone disease and 42.7 ± 12.3 min in acute cholecystitis. The comparative analysis of nociceptive activity in application of different types of pneumoperitoneum was conducted using the traditional analgesia/nociception index. The results obtained are presented in Table 1.

The analysis conducted indicated that argonoperitoneum application increased the

ANI by 5-7% and 16-18% in uncomplicated gallstone disease and acute cholecystitis, respectively.

Since our investigation involved the study of pain irritation intensity rather than analgesia adequacy analysis, it was more demonstrative to determine the reverse index for ANI, namely the NAI index, which is an indicator of pain impulsion: $NAI = 100 - ANI$. Dynamic changes in the NAI in the patients of the control group (Group 1 and Group 1a) turned out to be stereotyped (Fig. 1). At the beginning of surgical access formation and after gas insufflation into the abdominal cavity, an increase in nociceptive impulse was observed.

Figure 1. NAI dynamics; patient S (Case Record No 321518); Group 1.

During the main stage of surgery, it was corrected by opiate analgesic introduction. Though, an increase in nociceptive impulse was noticed once again at the end of surgery while recovering from anesthesia. Gas desufflation from the abdominal cavity does not have any significant effect on pain syndrome that leads to the necessity of analgesic administering in the postoperative period.

In the groups of patients, where argonoperitoneum was used, NAI dynamics was slightly different (Fig. 2).

It should be noted, that during the operation under conditions of argonoperitoneum, the nociceptive load did not exceed the limits of adequate analgesia. After surgery, the objective parameters of pain syndrome were low and did not require additional administration of analgesics.

Both pain irritant and the patient's preoperative excitement, systemic inflammation syndrome in acute cholecystitis, diet restrictions are supposed to affect the intensity of the body stress response. Therefore, serum cortisol level is the indicator that allows comparing different strategies of patients' management if the comparison groups are homogeneous. Dynamic changes in cortisol level may reflect the real picture of the impact of pneumoperitoneum type upon the operative stress intensity (Table 2).

At the beginning of this stage of investigation, we compared the medians of the cortisol level of four groups of patients in the initial stage, i.e., before gas insufflation. For this purpose, we applied the Kruskal-Wallis test. The test statistics was found to be 0.49; $p=0.78$. Since $p>0.05$, there is no statistically significant difference between the medians in the 95% confidence interval (CI). Hence, the initial values of cortisol blood levels did not differ considerably among various groups.

Figure 2. NAI dynamics; patient M (Case Record No 104319); Group 2.

Nevertheless, when comparing the median data of the four groups after gas insufflation into the abdominal cavity by means of the Kruskal-Wallis test, the test statistics was found to be 55.92 and $p<0.05$; thus, the data were statistically significantly different. Herewith, graphical presentation of the data distribution in the four groups clearly demonstrated significantly higher median values in the patients with carboxyperitoneum as compared to those with argonoperitoneum (Fig. 3).

Figure 3. Dynamic changes in serum cortisol levels in the control and experimental groups at observation stages.

Consequently, serum cortisol level in the patients suffering from gallstone disease with acute cholecystitis was higher than that in the patients

Table 2. Dynamic changes in cortisol blood level at different stages of surgery in patients of comparison groups depending on of pneumoperitoneum type.

Examination stage	Cortisol level, ng/ml, M $\pm$ SD; Me (0.5L; 0.5U)			
	Group 1 (n=30)	Group 1a (n=25)	Group 2 (n=25)	Group 2a (n=50)
Basic data	560 $\pm$ 51	589 $\pm$ 118	569 $\pm$ 126	580 $\pm$ 112
	516 (502; 583)	614 (543; 658)	517 (505; 615)	503 (501; 598)
Main stage of surgery	341 $\pm$ 61	530 $\pm$ 99	244 $\pm$ 65	323 $\pm$ 47
	406 (392; 413)	540 (498; 566)	239 (181; 286)	318.5 (197; 335)
End of surgery	312 $\pm$ 45	534 $\pm$ 97	223 $\pm$ 150	221 $\pm$ 30
	352 (325; 363)	497 (404; 542)	233 (204; 361)	205.5 (189; 250)

with uncomplicated forms of cholelithiasis. Further evaluation of serum cortisol level during surgery in each of the groups was conducted using the sign test. Whereupon, the null hypothesis was assumed as one in which the median difference of paired data equals 0; alternative hypothesis – the median difference does not equal 0.

In the patients of Group 1 who underwent general anesthesia under conditions of carboxyperitoneum, the comparison of basic data with those of the main stage of the operation provided the following test statistics: 2.77; $p=0.0056$ ($p<0.05$ – the null hypothesis deviated for $\alpha=0.05$, i.e. there was a difference between paired data in the 95% CI). Therefore, during the main stage of surgery, cortisol level was significantly lower than that during the previous stage (basic data). When comparing cortisol values at the main and final stages of the operation (after CO₂ desufflation), the test statistics = 3.62; $p=0.00029$. Thus, there was a statistically significant difference between these stages, namely cortisol level decreased at the end of surgery and anesthesia.

In the patients of Group 1a (acute cholecystitis), who received carboxyperitoneum during the operation, the comparison of basic data with those of the main stage of surgery provided the following test statistics: 4.48; $p=0.00000756$. Thus, there was a statistically significant difference between the paired data in the 95% CI, namely during the main stage, the level of stress hormone (cortisol) was lower than that at the beginning of the oper-

ation. When assessing the dynamics of changes in serum cortisol level at the main and final stages of surgeries, the test statistics was found to be 3.2; $p=0.0014$, i.e. there was an important and statistically significant difference between paired data of the groups, whereof it follows that at the end of surgery, cortisol level increased which might indirectly indicate intensification of pain irritation under carboxyperitoneum influence.

In the patients of Group 2 and Group 2a, who underwent cholecystectomy in argonperitoneum conditions, the comparison of basic data with those of the main stage of the operation provided the following test statistics: 4.48; $p=0.0000076$, which indicated a statistically significant decrease in cortisol level in comparison with basic data. While analyzing and comparing the data received at the final stage of the operation, test statistics was 0.21; $p=0.83$. Since $p>0.05$, we cannot ignore the null hypothesis for $\alpha=0.05$. No difference between paired data in the 95% CI indicated that cortisol level in the patients of Group 2 and Group 2a did not show any increase at the end of the operation in comparison with the data at the main stage of surgery.

Moreover, we conducted a comparative analysis of cortisol values between groups of patients at different stages of surgery.

Using the Mann-Whitney test criterion for comparing the medians of two different groups, it was found that at the time of the main stage of endoscopy, the result of the comparative analysis be-

tween Group 1 and Group 2 corresponded to $W=470.5$; $p=8.7E^{-8}$; $p<0.05$. Thus, there was a statistically significant difference between the medians of two groups in the 95% CI; according to the graphical presentation of data distribution in the groups, cortisol level was lower in the patients of Group 2, who underwent surgery under argonperitoneum conditions (Fig. 2). While comparing the data received at this stage of the operation in Group 2a and Group 1a, test statistics was $W=299.5$; $p=0.18$; $p>0.05$. Consequently, there was no difference between the medians of two groups in the 95% CI that proved the compatibility of blood cortisol levels in the patients of these two groups.

At the stage of surgery and anesthesia completion, we conducted the comparison of cortisol levels in the patients of Group 1 and Group 2 - $W=479.0$; $p=2.8E^{-8}$; $p<0.05$. Hence, there was a statistically significant difference between the medians of these groups in the 95% CI; thus, according to the graphical presentation, cortisol level was lower in the patients of Group. The comparison of cortisol levels in the patients of Group 2a and Group 1a at this stage of the observation provided the following evidence: $W=447.5$; $p=0.0000015$, thus convincingly proving a statistically significant difference in the 95% CI and significantly lower cortisol level in the patients of Group 2a.

Consequently, while investigating the dynamics of changes in serum cortisol level, there was found a significant baseline increase in all the three groups due to preoperative psycho-emotional stress, pain syndrome involvement, etc. At the main stage of endoscopic surgery, cortisol level decreased in comparison with basic data of the patient of all the groups, though most prominently in the patients of Group 1 and Group 2 patients, that was caused by both the elimination of psycho-emotional stress and complex protective effect of general anesthesia. Weak tendency in cortisol level decrease in the patients of Group 1a and Group 2a can be explained by a negative influence of other adverse factors inherent in these groups of patients, namely acute cholecystitis which is naturally accompanied by both systemic inflammation and pain syndrome. Considering the results obtained, it can be stated

that laparoscopic operations under argonperitoneum conditions are more optimal from the point of view of minimizing the pain syndrome and operational stress.

The causes of analgesic effect potentiation under argon effect have not been studied before. In the presence of inflammation, local acidosis is likely to be exacerbated by the effect of carbon dioxide. Having no chemical influence upon the peritoneum, argon reduces the local irritant effect of acidic compounds, thereby enhancing the effect of analgesic agents. To test the mentioned above hypothesis, we compared the acidity of peritoneal lavages in the patients of the experimental groups. With this aim, after completing cholecystectomy, the right subphrenic space was washed with 20 ml of sodium chloride saline solution by means of a laparoscopic aspirator. The pH of the aspirate fluid was evaluated using a laboratory pH-meter. The results obtained are presented in Table 3.

Table 3. Acidity (pH) of peritoneal lavages after cholecystectomy completion.

Group				p	p
1	1a	2	2a	(1-3)	(2-4)
(n=20)	(n=20)	(n=20)	(n=20)	(1-3)	(2-4)
1	2	3	4		
5.24	5.02	6.78	6.12	<0.01	<0.01
± 3.2	± 0.6	± 0.9	± 0.34		

The analysis of the pH-metry results showed that the patients, who underwent cholecystectomy under carboxyperitoneum conditions, presented with highly acidic lavages, while the patients, who underwent surgeries under argonperitoneum conditions, had acidity values close to neutral. Such pattern was characteristic for patients with both uncomplicated forms of gallstone disease and those suffering from acute cholecystitis.

The analysis of postoperative pain syndrome intensity was conducted by means of both the subjective NRS (Table 4, 5) and the number of Dexketoprofen injections within the first day after the operation (Table 6).

Thus, the obtained results proved that during the

Table 4. Pain syndrome intensity (according to the NRS scores) in the postoperative period in patients with uncomplicated gallstone disease.

Time after surgery	Group 1	Group 2	p
1 hour	4.14±0.56	2.18±0.24	<0.01
6 hours	5.24±1.31	2.83±1.12	<0.01
24 hours	3.43±1.12	1.85±0.21	<0.01

Table 5. Pain syndrome intensity (according to the NRS scores) in the postoperative period in patient with acute cholecystitis.

Time after surgery	Group 1a	Group 2a	p
1 hour	5.21±0.24	3.48±0.23	<0.01
6 hours	6.19±2.12	4.13±3.22	<0.01
24 hours	4.13±1.22	2.55±1.23	<0.01

Table 6. Number of injections of analgesic (Dexketoprofen) at the patients' request during the first 24 hours after the operation.

Groups	Number of injections	p (1-1a), p (2-2a)	p (1-2), p (1a-2a)
1 (n=202)	4.3±2.1		
1a (n=30)	5.2±1.1	<0.05	<0.05
2 (n=98)	3.1±0.9		
2a (n=30)	3.6±1.3	<0.05	<0.05

first day after cholecystectomy under carboxyperitoneum conditions in uncomplicated gallstone disease, pain syndrome persists at average indices during the first 6 hours and significantly reduces 24 hours after surgery. When using argonoperitoneum, a statistically significant decrease in the subjective sensation of pain was obtained at all time stages of assessment.

The analysis of the results obtained showed that, in acute cholecystitis, pain syndrome persists at higher rates than that in case of uncomplicated course of gallstone disease. Nevertheless, the use of argon for applying pneumoperitoneum in acute cholecystitis led to more favorable dynamics caus-

ing a statistically significant decrease in pain irritation.

According to data analysis, regardless of the type of pneumoperitoneum applied, acute cholecystitis was accompanied by a greater need for the administration of analgesics in the postoperative period in comparison with that in uncomplicated gallstone disease. However, in both uncomplicated form of gallstone disease and in acute cholecystitis, argonoperitoneum application statistically significantly reduces the need for analgesics during the first days of the postoperative period.

3. Conclusions

Both the objective criteria for pain syndrome and operative stress according to the results of ANI-monitoring and the analysis of the dynamics of serum cortisol concentration and the subjective assessment of pain syndrome conducted by questioning the patients and calculating the number of analgesic injections at the patient's request indicated the reduction in pain irritation in the parietal peritoneum in case of using argon as a pneumoperitoneum gas. The most probable explanation of this observation is the fact that argon application has less irritating effect as compared to carbon dioxide. In the presence of water, carbon dioxide produces carbonic acid, thereby changing the peritoneum pH. Being an inert gas, argon does not affect the peritoneum contributing to the absence of a local "peritoneal" component of postoperative pain. Argonoperitoneum with a direct insertion of the first trocar may be recommended to be introduced into practice of laparoscopic surgery.

4. Prospects of Further Researches

It is important to evaluate the effect of argonoperitoneum upon the duration of hospitalization and the quality of life of the patients. Both clinical and experimental comparative study of carbon dioxide and argon local effect upon the peritoneum is quite relevant as well. The extent of absorption of carbon dioxide by the peritoneum in either presence or absence of inflammatory changes and the ability of the

respiratory system and buffer systems to compensate for hypercapnia during prolonged laparoscopic operations should be evaluated.

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