

# THE ROLE OF MULTIMODAL ANALGESIA IN PATIENTS WITH TUBAL PATHOLOGY TREATED BY LAPAROSCOPIC SURGERY

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## REZUMAT

**Obiectiv:** Scopul lucrării este de a evidenția avantajele analgeziei multimodale în tratamentul durerii acute postoperatorii la pacientele operate laparoscopic pentru patologia tubară și consecințele acestei terapii asupra evoluției postoperatorii, comparativ cu metoda clasică de tratament a durerii postoperatorii. **Material și metodă:** Studiul este prospectiv și include 44 de paciente, împărțite aleatoriu în 2 grupe: lotul de studiu, 22 paciente, la care s-a practicat o schemă de analgezie multimodală (administrarea i.v. înaintea inducției anesteziei, de inhibitor-COX2, parecoxib sodic; infiltrarea de levobupivacaină la nivelul plasării fiecărui trocar, preincizional și instilarea intraperitoneală de levobupivacaină la începutul și la sfârșitul intervenției) și lotul martor, 22 paciente, la care s-a practicat o schemă de analgezie "la cerere" (nu s-au administrat substanțe analgetice non-opioide pre- sau intraoperator). Evaluarea intensității durerii postoperatorii s-a efectuat la ambele loturi atât în repaus-static cât și la mobilizare ușoară- dinamic, inițial la 4 ore apoi la 8, 12 și 24 ore. **Rezultate:** În primele 12 ore postoperator, scorul durerii în repaus la lotul de studiu a fost de  $0,04 \pm 0,21$  comparativ cu  $3,22 \pm 1,19$  la lotul martor, iar scorul durerii la mobilizare a fost de  $0,22 \pm 0,61$  la lotul de studiu comparativ cu  $5,4 \pm 1,22$  la lotul martor. La pacientele din lotul de studiu incidența grețurilor și vărsăturilor a fost mai scăzută, mobilizarea și externarea din spital a fost mai rapidă. **Concluzii:** La pacientele din lotul de studiu s-a constatat o bună analgezie postoperatorie, evidențiată prin scoruri ale durerii mici pe scara vizuală analogă (SVA), atât în repaus la pat, cât și la mobilizarea ușoară.

## ABSTRACT

**Objective:** The aim of the study is to highlight the benefits of multimodal analgesia in the treatment of postoperative pain in patients with tubal pathology operated by laparoscopic surgery compared to classical postoperative pain management. **Material and method:** This study is a prospective one and included a number of 44 patients operated by laparoscopic surgery for tubal pathology. The patients were randomly divided into two groups: the study group (22 patients) received pre- and intraoperative multimodal analgesia, which included a COX-2 inhibitor (parecoxib) i.v. before induction of anesthesia, levobupivacaine infiltration before skin incision and intraperitoneal administration of levobupivacaine at the beginning and at the end of the procedure, and the control group (22 patients) had general anesthesia without any pre- or intraoperative nonopioid analgesic. Evaluation of postoperative pain intensity was performed in both groups, at rest, static, and during mobilization, dynamic, at first at 4 hours and then at 8, 12 and 24 hours. **Results:** In the first 12 hours postoperatively the mean pain score at rest in the study group was  $2,98 \pm 0,53$  compared to  $4,66 \pm 1,15$  in the control group and the mean pain score during mobilization was  $3,81 \pm 0,88$  in the study group compared to  $5,91 \pm 1,47$  in the control group. Incidence of PONV was lower, mobilization and hospital discharge were faster for patients in the study group. **Conclusion:** Pre- and intraoperative multimodal management of postoperative pain resulted in lower VAS pain scores at rest and during mobilization compared to classical postoperative pain treatment.

**Key Words:** multimodal analgesia, visual analogue scale, tubal pathology, laparoscopic surgery

## INTRODUCTION

International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".

Effective perioperative pain management poses a significant challenge for healthcare practitioners and personnel (anesthesiologists, surgeons, nurses, physiotherapists); the responsibility for inadequate pain control is multifactorial in origin.<sup>1</sup>

The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the incidence of opioid-related adverse events. The rationale for this strategy is the achievement of sufficient analgesia due to the additive or synergistic effects between different classes of analgesics. This allows for a reduction in the doses of individual drugs and thus a lower incidence of adverse effects from any particular medication used for perioperative pain management.<sup>2-4</sup>

The aim of the study is to highlight the benefits of multimodal analgesia in the treatment of postoperative pain in patients with tubal pathology operated by laparoscopic surgery compared to classical postoperative pain management.

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## MATERIAL AND METHODS

Between November 2007 - June 2011 at the Municipal Emergency Hospital Moinești, 204 patients were operated laparoscopic for gynecological diseases. Of these, 44 patients were with tubal pathology. They were divided into: the study group (22 patients) received pre- and intraoperative multimodal analgesia and the control group, 22 patients, had general anesthesia without any pre- or intraoperative non-opioid analgesic.

At all patients, they were explained the purpose, technique and risks of study and consent were taken. Laparoscopic surgery was performed with general anesthesia.

Premedication with COX2-selective NSAID, intravenous Parecoxib, induction with Fentanyl, Diprivan, Atracurium and maintenance of anesthesia (Sevoflurane) were in accordance with expert advice regarding anesthesia in laparoscopic surgery.<sup>5</sup>

Postoperatively, for all the patients, analgesia was performed "on request" by a major-opioid, Morphine, or a nonopioid analgesic, used Perfalgan (paracetamol) 1g intravenous slowly diluted, or Algocalmin (metamizol) 1g intravenous slowly diluted, administered according to the intensity of pain reported by patient, quantitatively assessed on a visual analogue scale (VAS).

Particularly, for the patients in the study group was applied a multimodal analgesia scheme which included a COX-2 inhibitor (Parecoxib sodium 40 mg) i.v before induction of anesthesia, 0.25% Levobupivacaine infiltration before skin incision and intraperitoneal administration of local anesthetic (40 ml Levobupivacaine 0.25%) by gynecologist, in two stages: half the calculated volume was administered immediately after the creation of the pneumoperitoneum, and the other half at the end of the operation before the withdrawal of the trocars and intraperitoneal CO<sub>2</sub> exufflation.

The evaluation of postoperative pain intensity was performed in both groups at rest, static, and at mobilization, dynamic, first at 4 hours and then at 8, 12 and 24 hours.

Assessment of postoperative pain was done with pain score on visual analogue scale. VAS is practically the most used method for assessing postoperative pain, being the most sensitive. The patient indicates on a imaginary horizontal ruler marked from 0 to 10 cm, the appropriate pain position that she feels: 0 = no pain, 10 = unbearable pain. (Table 1)

At a superior pain level, more than 6 – 7 points on the VAS, patients received opioid - Morphine titrated intravenous (2 mg), supplemented with subcutaneous

administration of Morphine for the extension of analgesic effect.

At level pain between 3 and 6 points - titrated intravenous Morphine 2 mg + 40 mg Parecoxib sodium intravenously.

At an inferior pain level – less than 3 – the patients received Perfalgan (Paracetamol) 1g i.v or Algocalmin (Metamizole) 1 g.

Results were expressed as mean ± standard deviation. Statistical data processing was done with chi square (p <0.05 statistically significant), with a confidence interval (CI) = 95%.

**Table 1.** Visual Analogue Scale.

0	1	2	3	4	5	6	7	8	9	10
No pain										
Unbearable pain										

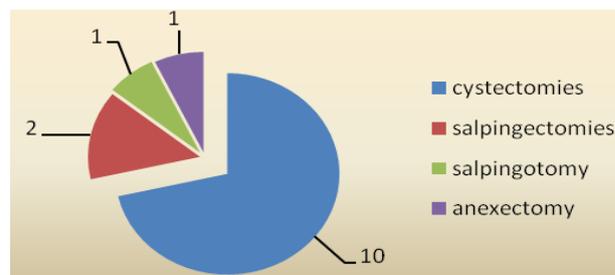
## RESULTS

The two groups of patients were relatively homogeneous, without any significant differences in demographic data (age, weight and anesthetic risk) and the anesthetic technique. (Table 2)

**Table 2.** The mean age of patients.

	Mean age (years)	Standard deviation (SD)	Minimum age	Maximum age
Study group	28,04	9,4	14	45
Control group	33,13	10,25	17	51

Laparoscopic treatment of these 44 patients involved in 14 cases of tubal cysts - 10 cystectomies, 2 salpingectomies, 1 salpingotomy and 1 anexectomy, in the case of the 15 ectopic pregnancies – 11 salpingectomies, 1 salpingotomy and 3 anexectomies and in the case of pelvic inflammatory disease patients – 4 salpingectomies, 2 salpingotomies, 4 anexectomies and 5 adhesiolysis. (Figs 1-3)

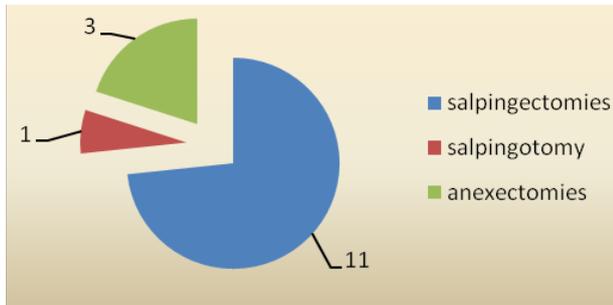


**Figure 1.** Laparoscopic treatment of tubal cysts.

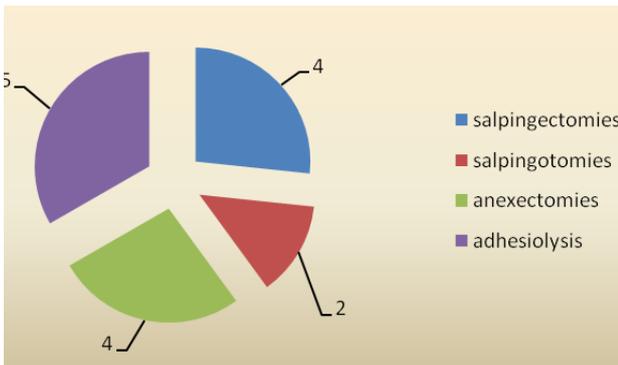
### Tubal cysts

Because of their development between foils broad ligament they requiring careful dissection to

avoid damage to the urethra and uterine pedicle, being practiced in 10 cases cystectomies after identification of the cleavage plan between the cyst wall and peritoneal leaf, 2 salpingectomies due to large size of cystic formations which greatly distorted tubal track, 1 salpingotomy when one of the formation poles was adhering to the tubal wall after adhesiolysis and 1 anexectomy (one patient aged 51 years) with sending the adnexal masses to anatomopathological examination.



**Figure 2.** Laparoscopic treatment of ectopic pregnancies.



**Figure 3.** Laparoscopic treatment of pelvic inflammatory disease.

### Tubal ectopic pregnancy

Salpingectomy was performed after evacuation of the hemoperitoneum for tubal pregnancies larger than 5 cm, in case of hemodynamic instability, if the fallopian tube was functional compromised, patients who wanted surgery sterilization having the family planning completed, if HCG > 100,000 mU/ml.

Salpingotomy with tube removal and preservation of pregnancy was performed in patients who desired fertility preservation, had a stable hemodynamic status, size of ectopic pregnancy was less than 5 cm, in the absence of contralateral tube pathology.

Anexectomy was performed because of coexisting ovarian pathology (2 cases of ovarian cystic tumor in patients 44 years and 41 years) and in one case in which hemostasis was difficult in the mesosalpinx.

### Pelvic inflammatory disease

Acute pelvic inflammatory disease – the pyosalpinx required salpingotomy with the discharge of the

purulent exudate after antibiotherapy, administered intravenously in 2 cases and 1 anexectomy with adhesiolysis for the adhesive syndrome and peritonitis. Tubo-ovarian abscess laparoscopically diagnosed at 3 patients required unilateral anexectomy after careful and difficult adhesiolysis of the intestinal loops, great omentum and sigmoid colon.

In the case of four patients hydrosalpinx was laparoscopically diagnosed due to complete tubal obstruction and salpingectomy was performed. The hydrosalpinx due to adhesions of the ovary fimbria was resolved by adhesiolysis (salpingo-ovariolysis) accompanied by lysis of extra-adnexial adhesions (omental and parietal or perihepatic adhesions if Fitz Hugh Curtis syndrome).

The mean operative time for laparoscopic surgery in the study group was 44.09 minutes with a range of 10 to 90 minutes and for control group patients was 53.4 minutes with a range between 25 and 100 minutes. (Table 3)

**Table 3.** The mean laparoscopic time (minutes).

	Mean laparoscopic time (minutes)	SD	Minimum operative time	Maximum operative time
Study group	44,09	19,12	10	90
Control group	53,4	19,66	25	100

### Analysis of postoperative analgesia efficiency

At the patients in the study group it was found a good postoperative analgesia, evidenced by lower pain scores, almost absent, on VAS, at rest and during mobilization. No patient required supplementation of analgesia. (Table 4)

**Table 4.** Pain scores of both groups.

Moment of determination	Study group		Control Group	
	VAS static	VAS dynamic	VAS static	VAS dynamic
4 hours	0,22	1,04	3,81	5,86
8 hours	0,04	0,95	4,72	6,94
12 hours	0,03	0,22	3,22	5,4
24 hours	0	0,09	1,68	3,27

At the control group, 22 patients with intravenous analgesia, "analgesia on request", the average postoperative pain recorded at 4 hours after admission in

intensive care unit was static  $1.13 \pm 3.81$  and dynamic  $5.86 \pm 1.28$ , average values of pain score very high compared with multimodal analgesia group. (Table 4) They show the presence of moderate to high postoperative pain, all the 22 patients (100%) requiring supplementation by administering an opioid, titrated intravenous morphine, at rest and during moderate mobilization.

The evaluation at 8 and 12 hours postoperatively indicates the presence of moderate-high pain, which require further analgesia supplementation.

A significant reduction in pain score was observed in measurements performed at 24 hours postoperatively. On visual analogue scale, postoperative pain score at rest was  $1.68 \pm 1.08$  and at mobilization:  $3.27 \pm 1.07$ .

This determined us to continue evaluating postoperative pain up to 48 hours postoperatively, when we found the net reduction at mobilization score on visual analogue scale:  $0.49 \pm 0.33$ .

Analgesic administration could be discontinued at 48 hours postoperatively, but further oral analgesic (per os) was recommended (the resumption of bowel movements was present), using a modest association of an opioid (codeine) with an NSAID, paracetamol, for another 24-48 hours until discharge.

Comparative analysis of the two methods of analgesia, multimodal and traditional, classical, "on request", at the two groups of patients operated by laparoscopic surgery, points out that the advantages of multimodal analgesia is not limited only to the absence or reduction of postoperative pain score in the first 24 hours postoperatively in the study group, but also that once this protocol is established, may result an improvement of postoperative evolution of patients.

The mobilisation of patients in the study group could be achieved much earlier, even at 4 hours postoperatively; that it is not passive mobilisation (respiratory gymnastics), but the active mobilisation of all patients in the study group. (Table 5)

**Table 5.** Mobilisation time (hours).

	Average	Min	Max	SD
Study group	4,22	1	10	2,28
Control group	21,95	14	32	4,32

Regarding the incidence of nausea and / or vomiting, it is in the control group of 72.72% (16 patients). They appear, although we given to all patients prophylactic antiemetic premedication (Dexamethasone 8 mg i.v).

Another crucial element is represented from a statistical point of view ( $p < 0.001$ ) between the two groups (16 patients in the control group versus one patient in the study group) in the incidence of nausea and/or vomiting.

Note however, that medication includes a steroid (a derivative of corticosteroid - anti-inflammatory and immunosuppressive) with strong antiemetic effects - Dexamethasone 8 mg (2 ml), intravenous, with 45-60 minutes before induction. In this context, oral rehydration was possible much earlier, at 24 hours postoperatively. Later, at 16-20 hours after surgery, they could eat: soups, juices, low-fat yogurt.

The presence of bowel movements was delayed at patients in the control group up to 36-48 hours. One possible explanation for the appearance of nausea and vomiting and for postoperative ileus up to 48 hours, can be the administration of an opioid, morphine. (Table 6)

**Table 6.** Bowel movement recovery time (hours).

	Average	Min	Max	SD
Study group	19,09	15	26	3,54
Control group	41,45	29	50	7,12

Time to discharge from intensive care unit and during hospitalization was significantly shorter in the study group, compared with the control group (Table 7).

**Table 7.** Influence of analgesia on the duration of hospitalization of patients.

	Study group	Control group	p
Discharge from the recovery room (hours)	$23,36 \pm 11,5$	$49,81 \pm 56,78$	0,01
Duration of hospitalization (days)	$3,22 \pm 1,15$	$6,22 \pm 2,99$	0,01

We made an analysis of physical and psycho-emotional comfort of all patients, expressed through satisfaction score after surgery. Of the 22 patients of the study group, 90.9% (N = 20), have given "excellent", while for 2 patients (9.1%) the score was "good".

For the control group, postoperative satisfaction score was reported as "good" by 4 patients, a total of 7 patients gave the score "satisfactory" (31.81%), while 11 patients appreciate the confort as "bad" - 50%

A comparative presentation of the postoperative evolution in the two groups of patients with gynecological laparoscopic surgery is shown in Table 8.

**Table 8.** Comparative presentation of postoperative evolution of patients.

Postoperative evolution	Study group	Control group
Mobilisation time (hours) – mean values	4,22	21,95
Incidence of nausea / vomiting (%)	4,54%	72,72%
Bowel movement recovery time (hours) – mean values	19,09	41,45
Surgical morbidity	0	0
ICU stay (hours) – mean values	23,36	49,81
Discharge from hospital after surgery (days) – mean values	3,22	6,22
Postoperative morbidity	0	0
Postoperative mortality	0	0
Postoperative satisfaction score (no. patients)		
Excellent	20	-
Good	2	4
Satisfactory	-	7
Bad	-	11

## DISCUSSION

Although laparoscopic surgery is less painful than the classic one, postoperative pain in the first 24 hours is intense and enough to justify the interest for many schemes of perioperative analgesia. Hohlieder et al. found that the worst pain after gynecological laparoscopic surgery was felt in the shoulder in 1% of the patients, two hours after surgery, but in 70% of the patients 24 hours after surgery.<sup>6</sup> The mechanism responsible for postoperative pain after laparoscopy still remains unclear.<sup>7</sup>

In this study, for multimodal postoperative analgesia we associated a COX2-selective NSAID i.v. and a local anesthetic, instilled intraperitoneally.

The mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase, which catalyzes arachidonic acid to prostaglandins and leukotrienes. Arachidonic acid is released from membrane phospholipids as a response to inflammatory stimuli. Prostaglandins establish the inflammatory response.<sup>8</sup>

Of selective NSAIDs, in this study was used Parecoxib sodium (Dynastat) 40 mg i.v.<sup>9</sup> Being a selective COX2 inhibitor in usual doses is lacking COX1 enzyme inhibition. Recently, it has been suggested that COX1 enzyme plays an important role in spinal cord pain processing and sensitization after surgery.<sup>10</sup> In contrast, paracetamol inhibits COX1 enzyme activity in the central nervous system and might exert an analgesic effect via NMDA (N-methyl d-aspartate) receptors in the spinal cord.<sup>11</sup> Part of its effect is thought to be mediated via a central serotonergic mechanism as has been shown in vivo. However, 5-hydroxytryptamine 3 receptor antagonists (5-HT<sub>3</sub> receptor antagonists) did not directly antagonize paracetamol in vitro, and thus an indirect mechanism has been postulated.<sup>12</sup>

Parecoxib, the first injectable COX-2 inhibitor, was introduced into clinical practice in 2001. It was found that preoperative administration of parecoxib was more effective than postoperative administration for postoperative pain relief in patients undergoing elective general surgical procedures such as appendectomy, open cholecystectomy and hernioplasty.<sup>13</sup> Parecoxib can be injected intravenously or intramuscularly with good patient tolerance. The lack of platelet inhibition allows COX-2 inhibitors such as parecoxib to be administered preoperatively. Parecoxib is now increasingly used in ambulatory or day-case surgery because it reduces opioid consumption, improves pain scores, and results in earlier hospital discharge and return to normal function.<sup>14</sup>

In a recent study from Finland, the  $\gamma$ -aminobutyric acid (GABA) analog pregabalin was used for postoperative pain relief in day-case laparoscopic gynecological surgery. However, it failed to demonstrate any advantage over diazepam 5 mg (active control) in reducing postoperative morphine usage.<sup>15</sup>

Intra-abdominal administration of local anesthetics (in combination with opioids to enhance their action) subscribes, with wound infiltration, among the analgesic methods used in laparoscopic gynecological surgery.<sup>16</sup>

Local anesthetic used was bupivacaine stereoisomers L-levobupivacaine (chirocaine), which blocks the transmission of painful stimulus by phrenic nerve fibers and also has in addition to bupivacaine (racemic mixture of stereoisomers L and D) a safer pharmaceutical and pharmacodynamic profile with lower neuro- and cardiovascular toxicity, meaning with a high safety and very good profile (stereoisomer D - responsible for toxicity).<sup>17,18</sup>

The mechanism of action is the interaction of levobupivacaine with cardiac ion channels Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>++</sup>, leading to selective blocking of these channels, preventing the nerve cell membrane depolarization and preventing the transmission of nervous influx. Levobupivacaine binds to specific receptors of Na<sup>+</sup> (sodium channels remain inactive in the closed position) blocking external pore of Na<sup>+</sup> channels. It results the impossibility of impulse propagation, due to not reaching action potential threshold.<sup>19</sup>

A comparison of our results concerning the analgesic efficacy with the results of previous studies is difficult because of different application times, routes, and dosages used. A study has compared ropivacaine 150 mg and bupivacaine 100 mg intraperitoneally (the maximum dose of ropivacaine is higher than that of bupivacaine, due to its reduced cardiac toxicity). The team found that ropivacaine reduced morphine usage

in the first 24 hours approximately four-fold. Both the local anesthetics reduced PONV.<sup>20</sup>

Jabbour-Khoury et al. reported that intraperitoneal spray of an aliquot of bupivacaine and NSAIDs, or intraperitoneal spray of local anesthetics following by intravenous NSAIDs resulted in significantly lower abdominal pain scores and incidence of vomiting after laparoscopic cholecystectomy, compared to the non-treatment group.<sup>21</sup> Meanwhile, Elhakim et al. revealed that a combination of intraperitoneal lidocaine and tenoxicam provided better analgesia on movement, and faster return of bowel function compared with intraperitoneal lidocaine and intravenous tenoxicam after laparoscopic cholecystectomy.<sup>22</sup>

Patients undergoing total abdominal hysterectomy under general anesthesia were randomized to receive a bilateral block of the abdominal wall with 1.5 mg/kg ropivacaine or placebo on each side just before incision.<sup>23</sup> PCA morphine use over the 48 h period after surgery was less in the ropivacaine group (27 mg) than in the placebo group (55 mg). Pain scores at rest and with movement were reduced in the ropivacaine group. The incidence of PONV did not differ between groups, but the incidence of sedation was reduced in the ropivacaine group. Patients undergoing total abdominal hysterectomy under general anesthesia were randomized into four groups and in whom a local anesthetic mixture (1% lidocaine, 0.25% bupivacaine, 2mg/ml adrenaline) was infiltrated under the skin: preoperative and postoperative; preoperative alone; postoperative alone; or placebo.<sup>24</sup> In this study, PCA Morphine consumption over 0–24 h and pain scores did not differ among the four groups. Perhaps the block of the abdominal wall (musculature and skin) is a more effective approach than skin infiltration.

The evaluation of pain intensity was achieved using visual analogue scale. VAS is considered to be quite accurate, reproducible and easy to use, although postoperative pain has an important subjective component.

## **CONCLUSIONS**

Postoperative evolution of patients in the study group, with multimodal analgesia, is obviously better than patients with classical analgesia, reducing complications resulting from prolonged immobilization, postoperative ileus duration and decreasing the incidence of postoperative nausea and vomiting.

These aspects contribute to a net improvement of postoperative evolution, increase satisfaction of patients and not least, decrease the overall cost.

Modern therapy of postoperative pain may be included in the so-called Fast Track Rehabilitation, next to early enteral nutrition and mobilisation, strategy which contributes essentially to improve postoperative evolution.

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