Evaluation of thoracic epidural analgesia in patients undergoing coronary artery bypass surgery – a prospective randomized trial

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Abstract

Introduction: Most recent studies tend to confirm the beneficial effect of thoracic epidural analgesia (TEA) in cardiac surgery.

Aim: To assess whether intensive care unit TEA has an influence on the perioperative course following low-risk coronary artery surgery.

Material and methods: This prospective, randomized trial was performed in patients scheduled for low-risk coronary artery surgery. Eighty patients undergoing off-pump or on-pump coronary artery bypass surgery were prospectively randomized to receive either combined general and epidural anesthesia or general anesthesia only. Time of postoperative ventilations and intensive care unit stay was compared between the groups. For all comparisons ($p < 0.05$) was considered statistically significant.

Results: The addition of TEA to general anesthesia significantly attenuated the stress response expressed by intraoperative heart rate, systolic blood pressure and cumulative doses of opioids. Time to the return of spontaneous respiration, time to extubation and time of stay in the postoperative care unit were all shorter in the study group, with no difference in hospital stay. Patients with TEA required midazolam less frequently (12.8% vs. 53.8%, $p < 0.001$). The percentage of patients given morphine in the study group was lower (46.2% vs. 89.7%, $p < 0.001$) and the mean dose given in patients receiving morphine was also lower (9.3 ±5.3 mg vs. 18.2 ±9.1 mg, $p < 0.001$).

Conclusions: Addition of TEA to general anesthesia shortens the return of respiratory function, duration of mechanical ventilation and ICU stay in the postoperative period after coronary artery surgery, providing comparable hemodynamic stability to general anesthesia alone.

Key words: anesthesia, epidural analgesia, coronary artery surgery.

Streszczenie

Wstęp: Ostatnie badania potwierdzają korzystny efekt zastosowania piersiowej blokady zewnątrzoponowej w kardiochirurgii.

Cel: Ocena, czy piersiowa blokada zewnątrzoponowa wpływa na przebieg okresu pooperacyjnego u chorych z grupy niskiego ryzyka poddawanych operacjom pomostowania naczyń wieńcowych.

Materiał i metody: Prospektywne badanie z randomizacją przeprowadzono u chorych z niskim ryzykiem zakwalifikowanych do operacji rewaskularyzacji naczyń wieńcowych. Osiemdziesięciu pacjentów zakwalifikowanych do operacji pomostowania tętnic wieńcowych w krążeniu pozaustrojowym lub bez użycia krążenia pozaustrojowego włączono do złożonego znieczulenia ogólnego i zewnątrzoponowego lub znieczulenia ogólnego. W analizowanych grupach porównano czas pooperacyjnej wentylacji i pobytu chorych na oddziale intensywnej terapii. Dla wszystkich przeprowadzonych obliczeń wartość współczynnika $p < 0,05$ uznano za statystycznie istotną.

Wyniki: Uzupełnienie znieczulenia ogólnego o blokadę zewnątrzoponową istotnie zredukowało odpowiedź stresową wyrażoną przez śródoperacyjną częstość akcji serca, skurczowe ciśnienie tętnicze i skumulowane dawki opioidów. Czasy powrotu oddechu własnego, pooperacyjnej wentylacji oraz pobytu na oddziale pooperacyjnym były istotnie krótsze w grupie badanej, nie było różnicy w czasie hospitalizacji. Pacjenci, u których zastosowano blokadę zewnątrzoponową, rzadziej wymagali zastosowania midazolamu (12,8% *vs* 53,8%, $p < 0,001$). Odsetek pacjentów przyjmujących morfinę w badanej grupie był niższy (46,2% *vs* 89,7%, $p < 0,001$), a średnia dawka morfiny była mniejsza (9,3 ±5,3 mg *vs* 18,2 ±9,1 mg, $p < 0,001$).

Wnioski: Uzupełnienie znieczulenia ogólnego o blokadę zewnątrzoponową skraca powrót prawidłowej funkcji układu oddechowego, czas trwania wentylacji mechanicznej i czas pobytu na oddziale intensywnej terapii po operacji tętnic wieńcowych, zapewniając porównywalną stabilność hemodynamiczną.

Słowa kluczowe: znieczulenie ogólne, analgezja zewnątrzoponowa, rewaskularyzacja naczyń wieńcowych.

Introduction

Interest in the use of thoracic epidural anesthesia (TEA) for cardiac surgery started in the mid-eighties with appreciation of high quality of the achieved perioperative anesthesia [1, 2]. Beattie *et al.* [3] confirmed that thoracic epidural anesthesia significantly lowers the frequency of tachycardia (which remarkably increases oxygen demand) in the early postoperative period and after performing a meta-analysis of available literature suggested that the use of this technique lowers the frequency of postoperative myocardial infarction [4]. Similar conclusions were presented by Liem *et al.* [5, 6] and Stenseth *et al.* [7], who additionally showed the beneficial impact of epidural anesthesia on respiratory function in the postoperative period. In 1996 Warner *et al.* [8] confirmed that TEA improves the diaphragm function in the perioperative period, preserving functional residual capacity (FRC) and decreasing the risk of focal pulmonary atelectasis, allowing for earlier extubation. It also emerged that even in patients with markedly decreased vital capacity (VC) the use of TEA would not lower the respiratory reserve. Moreover, one might expect a remarkable rise of VC, when an obstructive disorder is the leading symptom (provided that concentrated solutions of local anesthetics are avoided) [9].

Most recent studies tend to confirm this beneficial effect of TEA in cardiac surgery. In a meta-analysis of 31 studies identified up to 2010, TEA was shown to reduce the risk of postoperative supraventricular arrhythmias and respiratory complications [10]. Another systematic review (based on 66 randomized, case-matched studies) even proved that the use of TEA is associated with a reduction in mortality (number needed to treat = 70) and with an estimated risk of epidural hematoma of only 1 : 3552 [11].

Perioperative central blockade may additionally allow effective prevention of thromboembolic complications. Hypercoagulability in the postoperative period results from excessive sympathetic activity [12, 13]. Rodgers *et al.* [14] and Kehlet and Holte [15] in studies on large groups of patients concluded that the effect on hemostasis is one of the most important benefits resulting from the use of central blockade. Epidural anesthesia may also prevent perioperative digestive tract complications that occur as a result of visceral hypoperfusion and lead to increased permeability of digestive tract mucosa and endotoxemia [15–17].

This study presents a complex analysis and comparison of general and combined (general and epidural) anesthesia in patients undergoing elective coronary artery surgery performed either with or without extracorporeal circulation. We analyzed hemodynamic stability during the procedure and in the postoperative period, return of respiratory function after the operation and postoperative analgesia and sedation.

Aim

The aim of this study is to assess whether patients undergoing routine, low-risk cardiac surgery might benefit from adding TEA to general anesthesia.

Material and methods

The study was performed in a prospective, randomized fashion. It included patients with preserved good left ventricular function undergoing off-pump or on-pump coronary artery bypass surgery. The number of enrolled patients was 80. The recruitment period lasted 18 months. Patients were randomly assigned to two groups: group I ($n = 40$) had combined anesthesia – general and epidural (study group), while group II had only general anesthesia (control group). The study has been approved by the Ethical Committee of the Medical University of Silesia. Before the procedure all patients signed informed consent for both epidural anesthesia and for participation in the study. There were no patients who did not agree to TEA anesthesia.

Patients with contraindications for epidural anesthesia (i.e. purulent skin lesions, significant spine deformations, abnormal basic hemostasis parameters), with no informed consent, with chronic metabolic diseases (except diabetes), patients with advanced respiratory, renal or hepatic insufficiency, with symptoms of circulatory insufficiency or unstable coronary disease and urgent qualification for the procedure were excluded from the study. Advanced respiratory insufficiency was defined as forced expiratory volume 1 s (FEV_1) < 50% of normal volume and/or the presence of respiratory insufficiency in a preoperative arterial blood gas analysis. The study was discontinued if the following complications occurred: myocardial insufficiency requiring placement of an intra-aortic balloon pump or other methods of mechanical support, symptoms of acute myocardial ischemia, requirement for increased doses of inotropic drugs (dopamine and/or dobutamine up to 5 μg/kg/min was acceptable), cumulative time of extracorporeal circulation exceeding 180 min, marked drainage, deterioration in blood gases or other problems requiring elective extubation, and other circumstances not listed in the protocol that could affect postoperative sedation or elective extubation. In patients with any complications mentioned above only the operation period was analyzed.

All patients received standard preparation before the procedure. Coronary drugs (β-adrenolytics, calcium channel antagonists or nitrates, if appropriate) were continued with the last dose given at least 6 h before the procedure. Patients were assessed by the anesthesiologists at least 12 h before transfer to the operating theatre. Randomization was performed at this stage, by tossing a coin. Patients from the study group had an epidural catheter placed (under local anesthesia with lidocaine using the hanging drop technique) in a sitting position between Th1-Th2 or Th2-Th3 interspace. The catheters were inserted 3–4 cm into the epidural space using a Tuohy needle. End epidural line was secured with antibacterial filter and the catheter was flushed carefully with 3 ml of physiologic saline solution. All patients had their catheters inserted on the day before surgery or at least 6 h before the procedure.

All patients received standard oral premedication with midazolam. Bupivacaine in three different solutions was given as the local anesthetic during the study. Solution I

Table I. Demographic data

Parameter	Group I (n = 40)	Group II (n = 40)
Age [years]	60.4 ±6.9	58.8 ±10.1
Female sex	11 (27.5%)	9 (22.5%)
Height [cm]	167.6 ±7.5	169.4 ±6.7
Body weight [kg]	79.6 ±12.6	81.6 ±12.7
Body mass index [kg/m^2]	28.9 ±3.9	28.5 ±3.6
Body surface area [m^2]	1.9 ±0.17	1.9 ±0.16
Left ventricular ejection fraction (%)	52.8 ±8.9	51.8 ±10.6
EuroSCORE	2.4 ±1.58	2.7 ±1.97
CCS score	2.6 ±0.71	2.5 ±0.64
Off pump coronary artery surgery	16 (40.0%)	14 (35.0%)
Previous stroke	2 (5.0%)	2 (5.0%)
Recent myocardial infarction	21 (52.5%)	19 (47.5%)
Arterial hypertension	31 (77.5%)	31 (77.5%)
Carotid and/or peripheral artery disease	9 (22.5%)	11 (27.5%)
Diabetes	9 (22.5%)	14 (35.0%)
COPD	6 (15.0%)	2 (5.0%)

All differences in this table are not statistically significant.

contained 12 ml of 0.25% bupivacaine with fentanyl in a concentration of 10 µg/ml, solution II contained 40 ml of 0.19% (more exactly, 0.1875%) bupivacaine and fentanyl, and solution III contained 40 ml of 0.125% bupivacaine and fentanyl in a concentration of 6.25 µg/ml.

Before starting the induction of anesthesia, patients from the study received a test dose of 3 ml of solution I and were observed for the next 3 min to make sure no symptoms of subarachnoid anesthesia occured. After that, the remaining 9 ml of solution I were administered (6–8 ml in patients with height of less than 160 cm). This was followed by starting an infusion of solution II via the epidural catheter. The rate was started at 6 ml/h. Induction of general anesthesia was started 5 min after administering the initial dose of the drug.

Induction of anesthesia was identical in both groups, only with lower doses of fentanyl given to patients from the study group. All patients initially received fentanyl *i.v.* (group I received 2 µg/kg, group II received 5 µg/kg), then etomidate (0.2 mg/kg) and pancuronium (0.1 mg/kg). General anesthesia was maintained using inhalation of isoflurane. To ensure intraoperative analgesia group I received only epidural analgesia by means of solution II infusion, regulated within 6–10 ml/h according to the reaction of the circulatory system. In case of painful stimuli, additional small doses of fentanyl (1–2 µg/kg) were given. In group II fentanyl was administered throughout the procedure: an

initial dose of 5 µg/kg and subsequent doses as required, with the condition that the total dose of fentanyl should not exceed 35 µg/kg and the last dose should be given 1 h before the end of surgery at the latest. After closing the sternum, patients from both groups received 0.1 mg/kg *i.v.* of morphine for postoperative analgesia.

In group I, postoperative pain was managed with continuous infusion of solution III into the epidural space with the initial rate of 6 ml/h, kept in the range of 2–8 ml/h depending on the hemodynamic response and the intensity of postoperative pain. The epidural catheter was removed before discharging the patient from the postoperative unit.

Patients in group II received intravenous morphine for the management of postoperative pain. If the patient complained of pain, repeated injections of 2 mg morphine *i.v.* were given until sufficient analgesia was achieved. This procedure was also started in patients in group I, but only after achieving the upper limit of the epidural infusion rate (8 ml/h).

In case of excessive values of blood pressure and/or heart rate, patients were given 0.05 mg/kg *i.v.* morphine and the rate of nitroglycerin infusion was adjusted. In group I this procedure was performed again only after achieving the upper limit of the epidural infusion rate (8 ml/h). When patients complained of pain after extubation, 2 mg of *i.v.* morphine was given and this dose was repeated until adequate analgesia was achieved.

Study groups did not differ regarding demographic data, general health status or accompanying diseases (Table I).

Statistical analysis

Mean and standard deviation were used in the analysis of the data. The *t*-test, Mann-Whitney test or Fisher's exact test was used, as appropriate. Kaplan-Maier curves were used for comparison of the extubation times. Statistica 10.0 statistical software was used for statistical analysis. All findings with $p < 0.05$ were considered statistically significant.

Results

The use of epidural analgesia did not essentially change the hemodynamic parameters during the operation, but the heart rate remained significantly lower in group I for almost all the procedure (Fig. 1).

Smaller differences were recorded in values of systolic blood pressure, which reached significantly lower values in group I only after sternal dissection (Fig. 2).

Cumulative doses of intraoperative opioids and the proportion of patients requiring atropine or ephedrine were analyzed. Differences in cumulative doses were statistically significant. In group I the mean dose of *i.v.* fentanyl was only 4.9 µg/kg compared to 33.2 µg/kg in group II ($p < 0.001$). More patients in group I received ephedrine to correct the low blood pressure values during anesthesia (32.5% vs. 2.5%, $p < 0.001$).
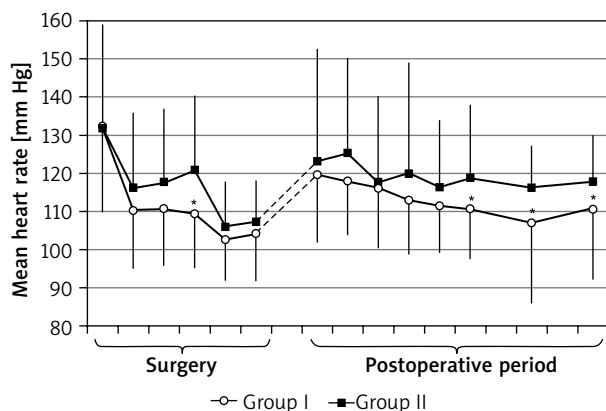
Fig. 1. Mean heart rate values during the operation and in the post-operative period
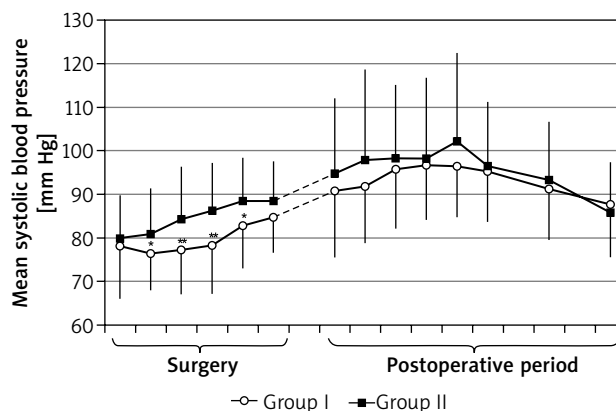

Fig. 2. Mean systolic blood pressure values in both groups

Table II. Values of arterial blood oxygen tension (paO_2) in mm Hg

Postoperative period	N	Group I	N	Group II	P-value
On arrival	39	115 ±54	39	138 ±40	< 0.01
After 2 h	39	118 ±36	39	128 ±31	NS
After 4 h	39	113 ±32	39	110 ±28	NS
After 6 h	39	118 ±49	39	120 ±27	NS
After 12 h	26	116 ±26	38	123 ±32	NS

Table III. Values of arterial blood carbon dioxide tension ($paCO_2$) in mm Hg

Postoperative period	N	Group I	N	Group II
On arrival	39	35 ±7	39	37 ±6
After 2 h	39	37 ±6	39	38 ±5
After 4 h	39	40 ±7	39	38 ±5
After 6 h	39	42 ±7	39	39 ±5
After 12 h	26	43 ±4	38	40 ±4

Table IV. Awakening and extubation times in study groups (counted from admission to postoperative unit)

Time periods	Group I (n = 18)	Group II (n = 18)	P-value
Time to return of spontaneous respiration [min]	216 ±158	479 ±175	< 0.001
Time to extubation [min]	301 ±187	591 ±191	< 0.01
Time of stay in the postoperative care unit [h]	18.8 ±7.4	27.1 ±19.4	< 0.001
Hospital stay [days]	6.2 ±2.3	5.8 ±1.1	NS

The analysis of the postoperative period was performed in 39 patients in each group since 2 patients were excluded from participation in the study according to the methodology. In group I, one patient (operated on with the use of extracorporeal circulation) was excluded because of a serious hemorrhage that occurred immediately after being transferred from the surgical theatre and required reoperation. One exclusion occurred also in group II (also in a patient operated on with the use of extracorporeal circulation) because of perioperative myocardial infarction diagnosed both in ECG and with elevated serum enzymes.

No differences between the groups were found regarding mean values of arterial oxygen and carbon dioxide tension, apart from the significantly higher paO_2 on arrival in group I (Tables II and III, respectively). Respiratory support was not needed at any stage of postoperative care after extubation in both groups.

Despite similar values of hemodynamic parameters and arterial and carbon dioxide tensions, significant differences were found in the return of spontaneous respiration, time to extubation and length of ICU stay (Table IV). The dynamics of weaning from mechanical ventilation and extubation are graphically shown in Figure 3.

Analysis of medications given in the postoperative unit revealed that patients with TEA required midazolam less frequently (12.8% vs. 53.8%, $p < 0.001$), but the mean dose given to patients receiving midazolam was similar (3.8 ±1.1 mg vs. 6.1 ±3.8 mg). The percentage of patients given morphine in the study group was lower (46.2% vs. 89.7%, $p < 0.001$) and the mean dose given in patients receiving morphine was also lower (9.3 ±5.3 mg vs. 18.2 ±9.1 mg, $p < 0.001$).

No deaths or significant complications were noted in either group and all patients were discharged from the hospital in good clinical condition. None of the patients required
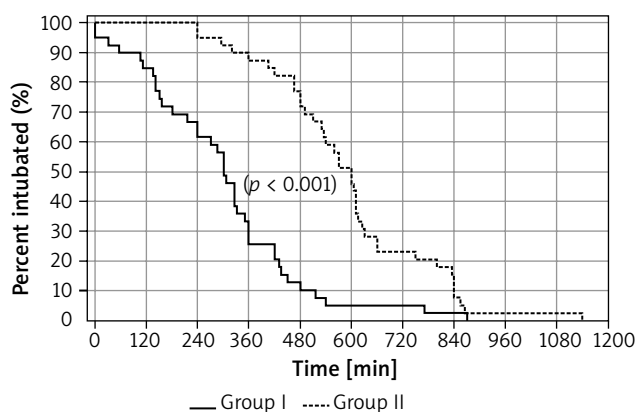
Fig. 3. Dynamics of weaning from mechanical ventilation and extubation

readmission to the postoperative unit, re-intubation, placement of an intra-aortic balloon pump, prolonged ventilation, reoperation or hemodynamic intervention during the hospital stay.

Discussion

The use of TEA during cardiac surgery is controversial. Despite being applied in cardiac surgery for over 20 years, it is still not in a position to be called a routine procedure for this kind of surgery. Recent literature shows renewed interest in the use of epidurals in cardiac surgery [10, 11, 18–21]. The reasons for that are complex and associated with ageing of the population of cardiac surgery patients, which is combined with the increased number of additional risks [20], especially chronic obstructive respiratory disease [22, 23]. There is growing evidence that TEA is associated with significant advantages that could potentially change the course of the early postoperative period [20, 21, 24], but the number of reports on epidurals in cardiac surgery is still insufficient. This was a reason to perform this prospective study.

Patients with severe chronic lung diseases constitute a special risk group among patients after cardiac surgery. It is well known that coronary artery surgery leads to significant impairment of the respiratory function and its return to efficiency, comparable to the state before the operation, may take up to 2 months [25].

It is also not clear when it is best to insert an epidural catheter before surgery. Some authors state that it is better to insert the catheter on the day prior to the operation [26–28], while others insert it immediately before the procedure [21, 29–31]. In our study, we decided to insert a catheter on the day before surgery or at least 6 h before the procedure.

Bupivacaine was chosen as the regional anesthetic for TEA as it is the easiest to access in Poland. Apart from bupivacaine, fentanyl (5 µg/ml) was used for central blockade, because of its better lipophilicity compared to morphine, which should result in rapid suppression of the nociceptive conductance at the level of posterior horns of the spinal cord [32]. We decided to use three different solutions at different stages of the postoperative course, aiming for a rea-

sonable compromise between sufficient intra- and postoperative analgesia and the risk of potential side effects (remarkable hypotension or severe respiratory depression). This resulted in hemodynamic stability throughout the procedure without any remarkable complications. It also seems that the strong nociceptive stimulation from the operation field was suppressed with that procedure and no substantial changes in heart frequency or blood pressure were recorded in key moments such as intubation, and skin or sternal incision.

The results show that patients after TEA not only woke up earlier, but less frequently required sedation in the immediate postoperative period. In the study group patients were extubated on average 5 h after the procedure compared to 10 hours in the control group ($p < 0.001$). These results are basically comparable to literature data though an direct comparison is difficult as methods of postoperative care are very variable among the authors reporting in this field [11, 20, 21]. Some authors applied naloxone in the postoperative period. It has a profound influence on return of consciousness and spontaneous ventilation [30, 33].

Another important aspect analyzed in the study was the evaluation of hemodynamic stability in the early postoperative period. The impact of central blockade on hemodynamics was studied in the 1950s and 1960s [34, 35]. Initially it was feared that the sympathetic blockade might affect the contractility of the heart muscle [36]. The turning point was the study on an animal model by Klassen *et al.* [37] from 1980, which showed a very beneficial impact of central blockade on redistribution of blood flow in cardiac muscle. Later studies by Davis *et al.* [38] and Groban *et al.* [39] only confirmed the positive influence of central blockade on cardiac muscle, simultaneously proving the beneficial impact of thoracic epidural blockade on cardiac muscle injury after acute closure of the coronary artery.

Values of basic hemodynamic parameters (heart rate and systolic blood pressure) were similar in the two groups, and the first significant differences in favor of the study group occurred 6 h after admission to the postoperative care unit. Blood pressure, together with heart rate, is the main factor increasing the oxygen requirement, which may directly affect myocardial ischemia, which in turn may lead to further complications such as perioperative myocardial infarction or arrhythmias. Transient myocardial ischemia in the early postoperative period occurred in 2 patients of the study group and in 5 of the control group, which did not affect the course of the postoperative period. These patients were electively extubated and transferred to the step-down unit for further therapy and rehabilitation, as ST elevation occurs relatively frequently in the early postoperative period and it is most often of no clinical significance [40]. Most recently, Jakobsen *et al.* [18] were able to prove that high thoracic epidural analgesia also improves cardiac performance. We were not able to confirm this finding on the basis of the advanced hemodynamic measurements performed in our study.

This study has several important limitations. Firstly, the sample size is far too small to draw firm conclusions,

although the number of patients was comparable to the most recent studies in this field [18, 20]. Secondly, for this study we selected a low-risk population, with satisfactory results regardless of the methods used. Finally, it is worth pointing out that all the selected endpoints are only secondary (similarly to many other studies in this field) [18, 20, 21]. The effect of TEA on the improvement of treatment outcomes has not been demonstrated. To date, such an effect (on mortality) has been confirmed only once, in the most recent meta-analysis pooling 6383 patients in 57 trials – probably due to the large sample size [11].

It should be noted that no complications that could result from insertion of the catheter into the epidural space were noted among the subjects of this study. It may therefore be concluded that a combination of general and epidural anesthesia during coronary artery surgery is safe and offers a remarkable benefit for the patients. It should be remembered, however, that this method should be used only by experienced and responsible anesthetists who are very experienced both in cardiac anesthesia and in performing epidural blockade. Therefore, TEA will probably never become a routine procedure in cardiac surgery.

Disclosure

Authors report no conflict of interest.

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