PECULIARITIES OF BILIARY FUNCTION OF THE LIVER IN THE DYNAMICS OF POLYTRAUMA IN THE EXPERIMENT

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Relevance. Severe trauma is accompanied by the development of multiple organ dysfunction and the insufficiency of internal organs. The dynamics of changes in the functional state of the liver didn't investigate fully. It is the central organ of detoxification of the body, whose activity occurs in close integration with other organs and systems of the body.

Objective is to find out the features of the biliary function of the liver in the dynamics of the developed model of polytrauma.

Materials and methods. Polytrauma was performed using 62 nonlinear white male rats weighing 180-200 g under conditions of thiopental-sodium anesthesia (40 mg 1kg-1 intraperitoneally). In surviving animals, the biliary function of the liver was studied in 2 h, 1, 3, 7, 14, 21, and 28 days after injury. For this purpose, the common bile duct was catheterized, and bile was collected for 1 hour in animals under thiopental-sodium anesthesia (60 mg kg-1). The rate of bile excretion and the concentration of total bile acids, cholesterol, direct and indirect bilirubin in the selected portion of bile were determined. Based on these data, the rate of excretion of the studied components of bile was calculated. Euthanasia of rats throughout the experiment was performed by total bloodletting from the heart after previous thiopental-sodium anesthesia (60 mg kg-1 intraperitoneally). The obtained digital data were subject to statistical analysis.

Results. In the conditions of experimental polytrauma, there is a violation of the biliary function of the liver. It is manifested in the period of an acute reaction to the trauma first (after 2 hours) by a significant it decreases, then (up to 1 day) development of polycholia - 1.52 times increased of bile secretion. Also increased excretion of the main components of bile, with their subsequent decrease to 7 days, development of the period of temporary improvement in 14 days with the repeated of exacerbation period in 21 days and approach to the norm - in 28 days.

The decrease in bile secretion corresponds to a period of shock, which is characterized by the centralization of blood circulation and reduced blood supply to the organs of the gastrointestinal tract. Increased bile secretion and excretion of main bile components in 1 day after a severe injury is associated with the increased biliary polarity of hepatocytes and unloading of the liver from endotoxins. It accumulates due to tissue damage, microcirculation, and hypoxia. Subsequently, the indicators of the biliary function of the liver changed by the identified patterns of lipoperoxidation deviations, antioxidant protection, cytolysis, and endogenous intoxication. The pathogenesis of biliary disorders is the damage of the endoplasmic reticulum membranes, where the synthesis of the main components of bile. As well as the development of edema of the organ, which prevents the outflow of bile.

Conclusion. The dynamics of the development of functional liver failure due to polytrauma coincides with the general pattern characteristic of the dynamics of other biochemical markers of traumatic disease. Namely: after 3 days of the post-traumatic period, there was a phase of maximum deepening of deviations of the studied indexes. After 7-14 days there was noted a phase of temporary improvement which is characterized by a change of indexes towards the norm. After 21 days there was a re-exacerbation of the pathological process. After 28 days the indexes changed towards the norm, but for most cases do not reach it.

This means that in a critical state of the body the organs and systems coupling is getting worse, which are remote from the site of injury. It can be considered as a factor of compensation and adaptation directed to the survival of the organism.

Keywords: rats, polytrauma, liver, bile

Relevance. In the structure of injuries in recent years, there has been a stable tendency to increase the frequency of combined injuries. It is 23.5-85.0% accompanied by the development of traumatic illness, and it is characterized by severe complications and high mortality [7]. Despite significant advances in the treatment of polytrauma victims, their effectiveness remains unsatisfactory. Therefore, many authors refer a comprehensive study of the pathogenetic mechanisms of the multiorgan dysfunction formation in conditions of polytrauma and traumatic illness to the main areas of modern theoretical and practical medicine [5].

In our previous works on the developed model of polytrauma [6], we showed that there is a pattern of the following indexes deviation. They are the dynamics of lipid peroxidation, antioxidant protection, cytolysis, and endogenous intoxication in the dynamics of the early and

late manifestations of the traumatic disease. It consists of the fact that after 3 days of the post-traumatic period, there is a phase of maximum deepening of deviations of the studied indexes. After 7-14 days there is noted a phase of temporary improvement which is characterized by a change of indexes towards the norm. After 21 days there is a re-exacerbation of the pathological process. After 28 days the indexes change towards the norm, but for most cases do not reach it.

It is known that a set of systemic abnormalities on the background of severe trauma are accompanied by the development of multiple organ dysfunction and insufficiency. Therefore, to increase the informativeness of our model of polytrauma, there was a task of determine its impact on the functional state of internal organs. In several publications for this purpose use indexes of a functional condition of a liver as a central body of

detoxification of an organism which activity occurs in close integration with other bodies and systems of an organism. [2].

Objective is to find out the features of the biliary function of the liver in the dynamics of the developed model of polytrauma.

MATERIALS AND METHODS

The experiments were performed using 62 nonlinear white male rats weighing 180-200 g, which were kept on a standard diet into vivarium. All manipulations with experimental animals were carried out following generally accepted bioethical standards of humane treatment of laboratory animals of international and national regulations for animal experiments: «European Convention for the Protection of Vertebrate Animals for Research and Other Scientific Purposes» (Strasbourg, 1986); «General ethical principles of animal experiments» (Ukraine, 2001), the Law of Ukraine «On protection of animals from cruel treatment» № 3447-IV (Ukraine, 2006).

Polytrauma was performed by our methodology developed, under conditions of thiopental-sodium anesthesia (40 mg 1kg⁻¹ intraperitoneally). In surviving animals, the biliary function of the liver was studied in 2 h, 1, 3, 7, 14, 21, and 28 days after injury. For this purpose, the common bile duct was catheterized, and bile was collected for 1 hour in animals under thiopental-sodium anesthesia (60 mg kg⁻¹). The rate of

bile excretion and the concentration of total bile acids, cholesterol, direct and indirect bilirubin in the selected portion of bile were determined. Based on these data, the rate of excretion of the studied components of bile was calculated. Euthanasia of rats throughout the experiment was performed by total bloodletting from the heart after previous thiopental-sodium anesthesia (60 mg kg⁻¹ intraperitoneally).

The obtained digital data were subject to statistical analysis. The significance of differences between experimental and control groups was evaluated using the program STATISTICA 10.0 (StatSoft, Inc., USA).

RESULTS AND DISCUSSION

The rate of bile excretion in 1 day of the post-traumatic period was significantly reduced by 37.9% compared to the control group by the influence of polytrauma (Table) ($p < 0,001$).

However, in 3 days this index increased sharply by 51.5% relative to control ($p < 0,001$) and more than 2 times relative to the previous observation period ($p < 0,001$). After 3 and 7 days, the rate decreased again and was statistically significantly lower than in the control (respectively by 11.7 and 9.8%, $p < 0,05$) and compared with 1 day of observation (respectively by 41.8 and 40, 5%, $p < 0,001$). After 14 days, the rate increased slightly and reached the level of control ($p > 0,05$). However, after 21 days there was a further decrease of 20.4% relative to the control group ($p < 0,01$). The index remained at the

Table

Dynamics of a biliary function of the liver in response to polytrauma (M±m)

2 hour (n=6)	1 day (n=6)	3 day (n=6)	7 day (n=6)	14 day (n=6)	21 day (n=5)	28 day (n=5)
The rate of bile excretion Control = (2,64±0,09) ml h ⁻¹ ·kg ⁻¹ (n=6)						
1,64± 0,08***	4,00± 0,16***	2,33± 0,07*	2,38± 0,04*	2,44± 0,11	2,10± 0,14**	2,34± 0,10**
The rate of bile acid secretion Control = (5,67±0,20) mg h ⁻¹ ·kg ⁻¹ (n=6)						
3,43± 0,29***	7,83± 0,49**	3,76± 0,17***	4,52± 0,16**	5,09± 0,09*	3,80± 0,34***	4,96± 0,32#
Cholesterol release rate Control = (1,13±0,07) mg h ⁻¹ ·kg ⁻¹ (n=6)						
0,534± 0,05***	1,65± 0,07**	1,13± 0,07	0,75± 0,06**	0,94± 0,11	0,98± 0,11	0,92± 0,05*
The rate of excretion of total bilirubin Control = (264,4±15,6) mkmol h ⁻¹ ·kg ⁻¹ (n=6)						
159,7± 10,0***	384,7± 22,5**	217,2± 10,1*	220,5± 8,7*	238,0± 13,3	202,5± 16,0*	228,3± 7,7#
The rate of release of direct bilirubin Control = (171,6±13,9) mkmol h ⁻¹ ·kg ⁻¹ (n=6)						
93,6± 5,3***	208,5± 12,8#	110,3± 10,5**	116,7± 7,7**	145,9± 11,5	98,8± 9,9**	128,1± 8,1*
The rate of secretion of indirect bilirubin Control = (92,8±6,2) mkmol h ⁻¹ ·kg ⁻¹ (n=6)						
66,1± 5,6**	176,2± 11,1***	106,9± 3,6#	109,85± 7,8	92,2± 6,5	103,7± 6,3	100,2± 9,6

Note: *# – significance of differences concerning the control group (* – $p < 0,05$; ** – $p < 0,01$; *** – $p < 0,001$; # – $p < 0,10$).

same level after 28 days and was 11.4% lower than in the control ($p < 0.01$). It is noteworthy that, starting from day 3 fluctuations in the value of the studied index in the dynamics of the post-traumatic period was insignificant ($p > 0.05$). It was statistically significantly different from the same, which was observed after 2 hours and 1 day after injury ($p < 0.05$).

The rate of excretion of bile components is responsible for the amplitude and vector at this rate of bile excretion. Thus, the rate of excretion of total bile acids (Table) in the acute period of injury (after 2 hours.) decreases by 39.5% ($p < 0.001$). After 1 day, this index increased significantly in the control group (by 38.1%, $p < 0.01$), as well as the previous observation period (2.3 times, $p < 0.001$). After 3 days, the index was re-decreased and was created by 33.7% less of control ($p < 0.001$) and by 52.0% regarding the previous observation period ($p < 0.001$). Then this index was increasing to 14 days, and after 7 days it is significantly greater than after 3 days (20.2%, $p < 0.05$); after 14 days greater than after 7 days (by 12.6%, $p < 0.05$). In all these terms of observation, the studied index was significantly lower than in the control (after 7 days - by 20.3%, after 14 days - by 10.2%, $p < 0.05$). After 21 days, there was a new decrease in the rate of excretion of total bile acids with bile by 25.3% during the previous observation period ($p < 0.01$), which was 33.0% lower than in the control ($p < 0.001$). After 28 days, this index was increased and had a slight tendency to decrease according to the control ($p < 0.10$). It statistically significantly was above the same value after 21 days of the post-traumatic period (30.5%, $p < 0.01$).

The rate of excretion of cholesterol with bile after 2 hours significantly decreased relative to the control group (Table) by 52.8% ($p < 0.001$). After 1 day, the index increased significantly: concerning the previous observation period 3.1 times ($p \leq 0.05$), concerning control by 46.0% ($p < 0.001$). After 3 days, the rate decreased and reached the level of control ($p > 0.05$). After 7 days, it continuously decreased and its average became 33.6% lower than in the control ($p < 0.001$), and relative to the previous observation period ($p < 0.05$). After 14-21 days, the rate increased and did not differ statistically significantly from the control group ($p > 0.05$). After 28 days the phase of the decline came again. The index was 18.6% lower than the control ($p < 0.05$). It should be noted that its level after 7-28 day did not differ significantly despite significant fluctuations in control ($p > 0.05$).

Similar deviations were observed in the magnitude of the rate of excretion of total bilirubin (Table). In 2 hours there was a statistically significant decrease in the value of this index relative to the control group (by 39.6%, $p < 0.001$). In 1 hour the index increased (by 45.5% relative to the control, $p < 0.001$, and 2.4 times relative to the previous observation period ($p < 0.001$). After 3-7 days, the index decreased again and became lower than the control by 17.9 and 16.6% ($p < 0.05$). After 14 days, the index increased although this was not statistically

significant compared to the previous observation period. But it reached the level of control ($p > 0.05$). After 21 days it was less by 23.4% than the control ($p < 0.05$), and after 28 days - by 13.7% ($p < 0.10$).

The rate of release of direct bilirubin (table) after 2 hours decreased relative to control by 45.5% ($p < 0.001$). After 1 day, it increased and exceeded the control level by 21.5% ($p < 0.10$) and the previous observation period by 2.2 times ($p < 0.001$). After 3 and 7 days, the index again became less than the control (respectively by 35.7 and 32.0%, $p < 0.01$). After 14 days, the index increased reaching the control level ($p > 0.05$) and then decreasing after 21 days (by 47.6% relative to control, $p < 0.01$) and increasing after 28 days - by 29, 7% relative to the previous observation period ($p < 0.01$). In the last observation period, the index was statistically significantly lower than in the control (25.9%, $p < 0.05$).

The rate of secretion of indirect bilirubin (Table) was similarly statistically significantly lower than in the control after 2 hours of the post-traumatic period (28.8%, $p < 0.01$). As in the previous terms, after 1 day the index increased and exceeded the control of 89.9% ($p < 0.001$), and the previous observation period in 2.7 times ($p < 0.001$). Then the rate decreased and, starting from 3 days did not differ from the control level ($p < 0.05$). After 3-28 days, the index also did not differ between the experimental groups ($p > 0.05$).

The obtained results indicate that the indexes of biliary function are characterized by a significant decrease after 2 hours of the post-traumatic period relative to the control group and a significant increase - after 1 day. It can be interpreted as a syndrome of «polycholia». The decrease of bile secretion corresponds to the period of shock, which is characterized by the centralization of blood circulation and reduced blood supply to the organs of the gastrointestinal tract [4]. Increased bile secretion and excretion of the main components of bile in 1 day after severe injury was observed in studies by other authors [2]. They have associated it with increased permeability of the biliary pole of hepatocytes and unloading of the liver from endotoxins accumulated due to tissue damage and microcirculation. Subsequently, the indexes of the biliary function of the liver changed according to the identified patterns of deviations of lipoperoxidation, antioxidant protection, cytolysis, and endogenous intoxication [6]. We can assume that in the pathogenesis of biliary disorders is the damage of the endoplasmic reticulum membranes, where the synthesis of the main components of bile [8], as well as the development of edema of the organ that prevents the outflow of bile [1].

Thus, in the conditions of the modeled polytrauma, there is a development of functional insufficiency of a liver. The formation of functional insufficiency of a liver obeys the general law which characteristic of deviation of other biochemical indicators (markers of a traumatic illness) from the third day. We can assume that in the critical state of the body the organs and systems coupling

is getting worse, which are remote from the site of injury. It can be considered as a factor of compensation and adaptation directed to the survival of the organism.

CONCLUSION

In the conditions of experimental polytrauma, there is a violation of the biliary function of the liver. It is manifested in the period of an acute reaction to trauma by the development of polycholia. Further decline of bile secretion and excretion of main bile components is shown up to 7 days. Their temporary improvement after 14 days with repeated reduction after 21 days, and approaching the norm in 28 days.

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ОСОБЛИВОСТІ ЖОВЧОВИДІЛЬНОЇ ФУНКЦІЇ ПЕЧІНКИ В ДИНАМІЦІ ПОЛІТРАВМИ В ЕКСПЕРИМЕНТІ

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Актуальність. Тяжка травма супроводжується розвитком поліорганної дисфункції і недостатності внутрішніх органів. Сьогодні не до кінця вивчена динаміка зміни функціонального стану печінки – центрального органа детоксикації організму, діяльність якого відбувається у тісній інтеграції з іншими органами і системами організму.

Мета: з'ясувати особливості жовчовидільної функції печінки в динаміці розробленої моделі політравми.

Матеріали та методи. На 62 нелінійних білих щурах-самцях, масою 180-200 г, виконували політравму в умовах тіопентало-натрієвого наркозу (40 мг•кг⁻¹ внутрішньочеревинно). У тварин, які вижили, досліджували жовчоутворювальну функцію печінки через 2 год, 1, 3, 7, 14, 21 і 28 діб після травми. З цією метою під тіопентало-натрієвим знечуженням (60 мг•кг⁻¹) у тварин катетеризували загальну жовчну протоку і збирали жовч протягом 1 год. Визначали швидкість жовчовиділення та концентрацію у виділеній порції жовчі сумарних жовчних кислот, холестеролу, загального, прямого і непрямого білірубину. На основі цих даних розраховували швидкість екскреції досліджуваних компонентів жовчі. Евтаназію щурів протягом усього експерименту проводили шляхом тотального кровопускання з серця після попереднього тіопентало-натрієвого наркозу (60 мг•кг⁻¹ внутрішньочеревинно). Отримані цифрові дані підлягали статистичному аналізу.

Результати. В умовах експериментальної політравми виникає порушення показників жовчовидільної функції печінки, що проявляється в період гострої реакції на травму спочатку (через 2 год.) суттєвим їх зниженням, потім (до 1 доби) розвитком поліхолії – в 1,52 рази збільшується швидкість жовчовиділення, посилюється екскреція основних компонентів жовчі, з подальшим їх зниженням до 7 доби, розвитком періоду тимчасового покращення через 14 діб з повторним періодом загострення через 21 добу і наближенням до норми – через 28 діб.

Зниження жовчовиділення відповідає періоду шоку, якому характерно централізація кровообігу та зниження кровопостачання органів шлунково-кишкового тракту. Підвищення жовчовиділення та екскреції основних компонентів жовчі через 1 добу після тяжкої травми пов'язано із збільшенням проникності біліарного полюсу гепатоцитів та розвантаженням печінки від ендотоксинів, які накопичуються внаслідок пошкодження тканин, порушення мікроциркуляції та розвитку гіпоксії. В подальшому показники жовчовидільної функції печінки змінювалися, відповідно до виявленої закономірності відхилень показників ліпопероксидації, антиоксидантного захисту, цитолізу та ендогенної інтоксикації. В патогенезі порушення жовчовиділення лежить пошкодження мембран ендоплазматичного ретикулуму, де відбувається синтез основних компонентів жовчі, а також розвиток набряку органа, що перешкоджає відтоку жовчі.

Висновок. Динаміка розвитку функціональної недостатності печінки, внаслідок політравми, співпадає із загальною закономірністю, характерною для динаміки інших біохімічних маркерів травматичної хвороби. А саме: через 3 доби посттравматичного періоду настає фаза максимального поглиблення відхилень досліджуваних показників. Через 7-14 діб відмічається фаза тимчасового благополуччя, яка характеризується зміною показників у бік норми. Через 21 добу виникає повторне загострення патологічного процесу. Через 28 діб показники змінюються в бік норми, проте в більшості своїй її не досягають.

Це свідчить, що в умовах критичного стану організму поглиблюється спряженість між органами і системами, віддаленими від місця пошкодження, яку можна розцінити як фактор компенсації та адаптації, спрямований на виживання організму.

Ключові слова: шури, політравма, печінка, жовчовиділення.

ОСОБЕННОСТИ ЖЕЛЧЕВЫДЕЛИТЕЛЬНОЙ ФУНКЦИИ ПЕЧЕНИ В ДИНАМИКЕ ПОЛИТРАВМЫ В ЭКСПЕРИМЕНТЕ

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Актуальность. Тяжелая травма сопровождается развитием полиорганной дисфункции и недостаточности внутренних органов. Сегодня не до конца изучена динамика изменения функционального состояния печени – центрального органа детоксикации организма, деятельность которого происходит в тесной интеграции с другими органами и системами организма.

Цель: выявить особенности желчевыделительной функции печени в динамике разработанной модели политравмы.

Материалы и методы. На 62 нелинейных белых крысах-самцах, массой 180-200 г, выполняли политравму в условиях тиопентал-натриевого наркоза (40 мг/кг внутривенно). У выживших животных исследовали желчеобразующую функцию печени через 2 часа, 1, 3, 7, 14, 21 и 28 суток после травмы. С этой целью под тиопентал-натриевым наркозом (60 мг/кг) у животных катетеризировали общий желчный проток и собирали желчь в течение 1 ч. Определяли скорость желчеотделения и концентрацию в выделенной порции желчи суммарных желчных кислот, холестерина, общего, прямого и непрямого билирубина. На основе этих данных рассчитывали скорость экскреции изучаемых компонентов желчи. Эвтаназию крыс в течение всего эксперимента проводили путем тотального кровопускания из сердца после предыдущего тиопентал-натриевого наркоза (60 мг/кг внутривенно). Полученные цифровые данные подлежали статистическому анализу.

Результаты. В условиях экспериментальной политравмы возникает нарушение показателей желчевыделительной функции печени, которое проявляется в период острой реакции на травму сначала (через 2 часа) существенным их снижением, затем (до 1 суток) развитием полихолии – в 1,52 раза увеличивается скорость желчеотделения, усиливается экскреция основных компонентов желчи, с последующим их снижением до 7 суток, развитием периода временного улучшения через 14 дней с повторным периодом обострения через 21 день и приближением к норме – через 28 суток.

Снижение желчеотделения соответствует периоду шока, для которого характерна централизация кровообращения и снижение кровоснабжения органов желудочно-кишечного тракта. Повышение желчеотделения и экскреции основных компонентов желчи через 1 сутки после тяжелой травмы связано с увеличением проницаемости билиарного полюса гепатоцитов и с разгрузкой печени от эндотоксинов, которые накапливаются в результате повреждения тканей, нарушения микроциркуляции и развития гипоксии. В дальнейшем показатели желчевыделительной функции печени менялись, в соответствии с выявленной закономерностью отклонений показателей липопероксидации, антиоксидантной защиты, цитолиза и эндогенной интоксикации. В патогенезе нарушения желчеотделения лежит повреждение мембран эндоплазматического ретикулума, где происходит синтез основных компонентов желчи, а также развитие отека органа, препятствующего оттоку желчи.

Вывод. Динамика развития функциональной недостаточности печени, вследствие политравмы, совпадает с общей закономерностью, характерной для динамики других биохимических маркеров травматической болезни. А именно: через 3 суток посттравматического периода наступает фаза максимального углубления отклонений исследуемых показателей. Через 7-14 суток отмечается фаза временного благополучия, которая характеризуется изменением показателей в сторону нормы. Через 21 день возникает повторное обострение патологического процесса. Через 28 суток показатели изменяются в сторону нормы, однако в большинстве своем ее не достигают.

Это свидетельствует, что в условиях критического состояния организма углубляется сопряженность между органами и системами, удаленными от места повреждения, которую можно расценить как фактор компенсации и адаптации, направленный на выживание организма.

Ключевые слова: крысы, политравма, печень, желчеотделение.