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ЗНАЧЕННЯ АКТИВАЦІЇ ЦЕНТРАЛЬНИХ ХОЛІНЕРГІЧНИХ СИСТЕМ ПРИ ЧЕРЕПНО-МОЗКОВІЙ ТРАВМІ

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Актуальність. При черепно-мозковій травмі (ЧМТ) активність центральних холінергічних систем (ЦХС) пригнічується, знижується вивільнення ацетилхоліну та експресія холінергічних рецепторів. Відновлення холінореактивності є актуальним напрямком досліджень та можливого терапевтичного впливу.

Мета: визначити вплив активації ЦХС на летальність, неврологічні порушення та активність гіпофізарно-кортикоадреналової системи (ГКАС) у гострому періоді ЧМТ.

Матеріали та методи. ЧМТ моделювали при вільному падінні вантажу на фіксовану голову тварини. Для активації ЦХС щурам до травми вводили холіну альфосцерат (гліатілін; 6 мг/кг), у контрольній групі вводили фізіологічний розчин. Неврологічний дефіцит оцінювали за 100-бальною шкалою Тодда. У плазмі крові через 3, 24, 48 і 72 годин після травми імуноферментним методом визначали вміст адренокортикотропного гормону та кортикостерону. Результати статистично обробляли із застосуванням програм SPSS 11.0, MedStat, MedCalc.

Результати. Летальність у контрольній групі склала 25,0%, у групі з активацією ЦХС летальних випадків не було ($p<0,05$). Неврологічний дефіцит у групі з активацією ЦХС був виражений достеменно менше порівняно з контролем на всіх термінах спостереження. Вміст гормонів мав схожу динаміку – сягав максимуму через 24 години і відновлювався через 72, але при активації ЦХС приріст був у 1,4-1,5 рази меншим ($p<0,05$). Отже, використання холіну альфосцерату для модулювання активності ЦХС призводило до зниження летальності та неврологічного дефіциту у гострому періоді ЧМТ, що супроводжувалося стабілізуючим впливом на ГКАС.

Висновок. Встановлено важливу роль ЦХС у реалізації посттравматичної стресової реакції ГКАС, а також можливість її фармакологічної корекції холіном альфосцератом.

Ключові слова: центральні холінергічни системи; експериментальна черепно-мозкова травма, холіну альфосцерат

Актуальність. Одно з важливих місць у структурі летальності в усьому світі посідає черепно-мозкова травма (ЧМТ), від якої щорічно у світі гине до півтора млн. людей, а 2,4 млн. отримують інвалідність [1, 2]. В Україні ці показники суттєво перевищують такі у Європі, що має чітку тенденцію до зростання [3, 4].

Патогенетична послідовність подій, що викликані ЧМТ, включає некроз, гліоз та апоптоз, дифузне аксональне пошкодження та демієлінізацію, нейрозапалення та нейродегенерацію [5]. Необхідно відзначити, що найбільше значення для формування основних причинно-наслідкових зв'язків має перший гострий період і адекватність реакції центральних медіаторних систем, зокрема – центральних холінергічних (ЦХС) [6, 7].

Пускове значення для запуску процесів пошкодження має первинна ішемія тканини, яка є тригерним механізмом дегенерації і загибелі нейронів [8]. За умов ЧМТ безпосередньою причиною ішемії є механічне пошкодження, яке руйнує крупноклітинні нейрони та їх відростки, призводе до розривів судин і проявляється контузією мозку, внутрішньочерепними крововиливами, дифузним аксональним пошкодженням [5]. Ключова роль на цьому етапі належить кальпаїну (сімейство цитозольних нейтральних Ca^{2+}-активованих цистеїнових протеаз), який запускає нейродегенерацію і апоптоз [9]. Вторинна фаза включає каскади нейрохімічних і нейрометаболічних подій, апоптоз нейронів у відділених ділянках мозку; опосередковується каспазами і проявляється внутрішньочерепною гіпертензією, запаленням, набряком і гіпоксією мозку [9, 10].

Одним з основних медіаторів ЦНС є ацетилхолін, який діє через мускаринові (М-) та нікотинові (N-) рецептори, які широко представлені у головному мозку [11, 12]. М-рецептори зв'язані з G-білками і підвищують вміст внутрішньоклітинного кальцію та знижують утворення циклічного аденозинмонофосфату (цАМФ). N-рецептори є іонними каналами, серед яких найбільше регуляторне значення належить Ca^{2+}-іонним каналам (підтип альфа7), які регулюють нейропластичність, когнітивні процеси, мають нейропротекторні властивості [13, 14].

Відомо, що при ЧМТ активність ЦХС пригнічується, знижується вивільнення ацетилхоліну та експресія холінергічних рецепторів, натомість ак-

тивність ацетілхолінестерази збільшується [15, 16]. Показано, що при ЧМТ введення холіноміметика цитидин-5'-дифосфату холіна покращує когнітивні здібності в експерименті і вивільнення ацетилхоліну [17]. Необхідно зазначити, що цей препарат активує переважно нікотинові альфа7-холінорецептори [18]. Також експериментальні дослідження з використанням блокаторів ацетилхолінестерази галантаміну [11] та донепезилу [19] мали позитивні результати: препарати підсилювали нейрогенез та покращували відновлення когнітивних функцій після ЧМТ. Однак, вплив донепезилу не був підтверджений у іншій роботі [20].

Мета: визначити вплив активації ЦХС на летальність, неврологічні порушення та активність гіпофізарно-кортикоадреналової системи (ГКАС) у гострому періоді ЧМТ.

МАТЕРІАЛИ ТА МЕТОДИ

Дослідження проведено на 64 білих щурах-самцях лінії Вістар масою 200-215 г. Строго дотримувалися умов Гельсінкської декларації (Генеральна асамблея Всесвітньої медичної асоціації, 2008 р.), норм та принципів Європейської конвенції про захист хребетних тварин, що використовуються для дослідницьких й інших наукових цілей.

Холінергічний вплив на ЦНС моделювали шляхом введення холіну альфосцерату («Гліатілін», ITALFARMACO, S.p.A.; Італія) – холіноміметику центральної дії, який посилює передачу імпульсів у холінергічних нейронах, поліпшує нейропластичність клітин, функцію рецепторів та синаптичну передачу. З урахуванням періодів накопичення активної речовини та напіврозпаду, кліренсу виведення, допустимої добової дози і з розрахунку на середню масу тварини препарат вводили за 24, 12, 6 та 1 годину до моделювання ЧМТ внутрішньоочеревенно в дозі 6 мг/кг. У контрольній групі за такою ж схемою вводили фізіологічний розчин.

ЧМТ завдавали стандартним методом при вільному падінні металевого вантажу на фіксовану голову тварини [21]. Вантаж являв собою круглий металевий стрижень масою 50 г, який вільно пересувався продовж металевої трубки довжиною 65 см, фіксованою строго перпендикулярно на металевій станині. З використанням поверхневого ефірного наркозу голову тварини фіксували під вертикально розташованою металевою трубкою таким чином, щоб отвір трубки знаходився вздовж сагітального шву та симетрично йому на 5 мм вперед від інтраурикулярної лінії. Вантаж вільно падав продовж трубки та здійснював миттєвий удар по склепінню черепа. За нашими попередніми даними ця модель давала змогу отримати чітко стандартизовану ЧМТ середнього ступеню [21]. Патологоанатомічне дослідження показало, що у тварин моделювалася закрита ЧМТ за наявністю підшкірної гематоми, без зсуву головного мозку та з розтрощенням кори скроневих і тім'яних часток у зоні удару та у зоні протиудару – основи лобових і скроневих часток. У речовині головного мозку спостерігали чисельні дифузні дрібноточкові крововиливи.

Для оцінки тяжкості ЧМТ була обрана 100-бальна шкала визначення неврологічного дефіциту [21], за якою проводили окрему оцінку (у балах) рівня свідомості – 0-20 балів; стану рефлекторної сфери, що включав ширину і реакцію зіниць на світло, рогівковий рефлекс, слух, м'язовий тонус тулуба та кінцівок – 0-28 балів; дихання – 0-12 балів; рух та локомоторні функції – 0-25 балів, а також деякі поведінкові реакції зі здатністю виконувати елементарні функції – 0-15 балів.

У плазмі крові, отриманій через 3, 24, 48 і 72 годин після ЧМТ, імуноферментним методом визначали вміст гормонів гіпофізарно-кортикоадреналової системи (ГКАС) – адренокортикотропного гормону (АКТГ) та кортикостерону (КС). Вміст речовин визначали за інструкцією до наборів реактивів від компанії-виробника (DSL; США). Кількісно інтенсивність забарвлення досліджуваних зразків оцінювали на імуноферментному аналізаторі Multiscan EX («Thermo Electron Corp.»; Фінляндія). Отримані результати піддавали статистичній обробці з використанням пакету ліцензованих програм для проведення прикладної статистики SPSS 11.0, MedStat, MedCalc (MedCalc SoftWare bvba, 1993-2013).

РЕЗУЛЬТАТИ ТА ЇХ ОБГОВОРЕННЯ

У гострому періоді ЧМТ летальність у контрольній групі склала 25,0% тварин, тоді як у групі з активацією ЦХС летальних випадків зафіксовано не було ($p<0,05$). Неврологічний дефіцит у тварин після ЧМТ мав тенденцію до зростання, що у групі з активацією ЦХС було виражено достеменно менше на всіх термінах спостереження (табл. 1).

Отже, початкова активація ЦХС попереджувала неврологічні порушення після ЧМТ, однак у динаміці спостереження неврологічний дефіцит мав позитивну динаміку.

Таблиця 1

Динаміка неврологічного дефіциту після ЧМТ (балів; M±m)

Група	Час після травми			
	3 години	24 години	48 годин	72 години
Контрольна	25,6±4,2	32,8±2,5	42,3±2,2	51,3±3,0
Активація ЦХС	6,8±0,6*	7,3±0,5*	12,5±1,3*	16,8±1,7*

Примітка. * – $p<0,05$ у порівнянні з контрольною групою

Таблиця 2

Динаміка вмісту гормонів гіпофізарно-кортикоадреналової системи після ЧМТ (M±m)

Група		До травми	Час після травми			
			3 години	24 години	48 годин	72 години
АКТГ, пмоль/л	контроль	28,3±5,4	37,7±2,3*	57,2±6,4*	32,3±5,6	21,5±2,7
	активація ЦХС		31,3±3,2	42,2±4,3*#	37,3±4,5	27,4±3,8
КС, нмоль/л	контроль	263±13	354±24*	621±35*	424±27*	241±17
	активація ЦХС		285±21#	403±28*#	314±25#	262±11

Примітки: * – p<0,05 у порівнянні зі значеннями до травми; # – p<0,05 у порівняні з контролем на відповідному терміні

Вміст АКТГ у контрольній групі після ЧМТ (табл. 2) підвищувався з максимумом через 24 години (p<0,05), що вказувало на активацію нейросекреторного процесу у центральній ланці ГКАС після ЧМТ та пояснювалося посттравматичною стресовою реакцією [22]. Через 72 години вміст гормону повертався до початкового значення. Вміст КС через 3 години після травми перевищував контрольні значення у 1,3 рази, а через 24 години вже у 2,4 рази (p<0,05). Як і вміст АКТГ, через 72 години вміст КС відновлювався до початкового рівня. Таким чином, у гострому періоді ЧМТ була відзначена активація як центральної, так і периферичної ланок ГКАС, яка згодом відновлювалася.

На відміну від цього, при активації ЦХС реакція ГКАС характеризувалася більш стабільним вмістом гормонів. Як і у контролі, АКТГ мав односпрямовану з КС реакцію: максимальне збільшення через 24 години з подальшим поверненням до початкових значень. Але приріст вмісту обох гормонів через 24 години після травми був суттєво менш вираженим, ніж у контрольній групі – у 1,4-1,5 рази; p<0,05; (табл. 2). Такий результат вказував на помірну реакцію ГКАС при активації ЦХС та протективний вплив активації ЦХС.

Таким чином, використання центрального холіноміметіка для модулювання активності ЦХС призводило до зниження летальності та неврологічного дефіциту у гострому періоді ЧМТ, що супроводжувалося стабілізуючим впливом на одну з основних адаптивних нейроендокринних ланок – ГКАС. Її адекватна активація забезпечує формування захисних компенсаторно-пристосувальних реакцій, спрямованих на підтримку серцево-судинної діяльності, адекватної перфузії тканин киснем та енергозабезпечення [22].

Отриманий результат вказує на важливу роль ЦХС у реалізації посттравматичної стресової реакції, а з іншого боку, – підтверджує можливість її фармакологічної корекції з використанням центрального холіноміметіка холіну альфосцерату, що може обмежувати надмірну активацію нейроендокринної системи, зменшувати летальність і неврологічний дефіцит.

В плані обговорення отриманих результатів необхідно зазначити, що центральні холінорецептори є складними багатомірними білками, які мають всі структурні елементи для перетворення хімічного сигналу, зазвичай локального підвищення концентрації позаклітинного ацетилхоліну, в електричний сигнал, викликаний відкриттям іонного каналу, та поводять себе як типові, але дуже складні аллостеричні машини [23]. Холінорецептори представляють собою суперсімейство пентамерних ліганд-керованих іонних каналів, яке включає рецептор 5-гідрокситриптамін, здатний інгібувати аніон-селективну γ-аміномасляну кислоту типу А (ГАМК-АR), гліцінові рецептори (GlyR) і глутамат-керований хлорідний канал (GluCl) [24]. Відомо, що активність холінорецепторів аллостерічно модулюються мембранними ліпідами, вільними жирними кислотами, стероїдами, вміст яких у мозковій тканині при ЧМТ різко збільшується [5-8].

Отже, саме пошкодження складної структури холінорецепторів та їх модулюючого впливу на інші нейрохімічні системи є фактором первинного посттравматичного пошкодження, що може пояснювати відмічене багатьма дослідженнями пригнічення ЦХС при ЧМТ [11, 13, 15].

В умовах ЧМТ особливе значення має широке розповсюдження холінорецепторів у ЦНС, що показано для гіпокампу, мигдалини, гіпоталамусу, лобової кори і медіодорсального ядра таламуса [25]. Гостре і хронічне системне введення нікотину та його аналогів в ці структури значно покращувало робочу пам'ять в лабіринті і гальмувало амнестичні ефекти антагоніста NMDA-глутаматних рецепторів дізоцілпіна, що мало довготривалий ефект [25]. Таким чином, виявлене нами зниження летальності та неврологічного дефіциту після ЧМТ на тлі введення холіну альфосцерату пояснюється важливою роллю ЦХС у реалізації адаптивних реакцій, доводить патогенну значущість їх гальмування та обґрунтовує необхідність відновлення холінергічної медіації у гострому посттравматичному періоді.

Відомо, що вісь гіпоталамус-гіпофіз-наднркові залози ініціює основну ендокринну відповідь на порушення гомеостазу [22]. Центральні холінергічні механізми активують цю вісь, що абсолютно необхідно як для базального, так і для викликаного стресом вивільнення глюкокортикоїдів з кори надниркових залоз [26]. Нейроендокринні клітини, що розташовані у медіальній парвоцеллюлярній частині паравентрикулярного ядра (ПВЯ) гіпоталамуса, ви-

діляють кортикотропін-рілізінг-гормон (КРГ) в гіпоталамо-гіпофізарну портальну систему, що індукує секрецію АКТГ клітинами передньої долі гіпофіза. Нейрони, які експресують КРГ, широко поширені в неокортексі, лімбічній системі і стовбурі мозку, що стосується переважно префронтальної, поясної та острівкової частин кори головного мозку, центрального ядра мигдалини, гіпоталамусу, центральної сірої речовини, парабрахіального ядра, блакитної плями і ядра солітарного тракту [27]. Ацетилхолін індукує вивільнення КРГ у гіпоталамусі, а антагоністи нікотинових рецепторів його інгібують. У щурів гостре системне введення нікотину активує синтез КРГ у нейронах ПВЯ, що збільшує плазмовий рівень АКТГ і КС [27]. Таким чином, ЦХС мають безпосередній вплив на гіпоталамічну регуляцію ГКАС. Протективний вплив введення холіну альфосцерату, що було показано у даному дослідженні, підтвердив важливість відновлення медіаторних відношень при ЧМТ та показав розбалансованість нейрохімічних механізмів, яке проявлялося надмірною активацією ГКАС. У наших попередніх публікаціях показано, що гіперактивація нейроендокринних систем при ЧМТ призводе до перенапруження компенсаторних механізмів та їх виснаження [7, 22].

Порушення функції ЦНС, що є наслідком ЧМТ, включають холінергічні механізми [28]. Показано, що після контузійної травми кори головного мозку знижувалася щільність холінергічних і глутаматних NMDA-рецепторів, а також експресія кальцієвих каналів, що особливо стосувалося підтипу альфа7-холінорецепторів. Саме їх висока кальцієва проникність пов'язана з нейродегенерацією та значним неврологічним дефіцитом після ЧМТ [28]. Дефіцит експресії альфа7-холінорецепторів сприяє когнітивним порушенням при ЧМТ, тоді як агоністи нікотинових рецепторів відновлюють цю недостатність та призводять до значного когнітивного поліпшення в порівнянні з контрольною групою [29]. Використання аллостерічного модулятора альфа7-холінорецепторів AVL-3288 покращувало когнітивні функції, зокрема робочу пам'ять у водному лабіринті, та попереджало атрофію гіпокампу після перкусійній ЧМТ. Це дозволило встановити, що посилення холінергічної передачі за рахунок позитивної аллостерічної модуляції альфа7-холінорецепторів може бути новим терапевтичним засобом попередження та лікування порушень вищої нервової діяльності при ЧМТ.

Крім того, специфічна активація альфа7-холінорецепторів знижує проникність гематоенцефалічного бар'єру після експериментальної ЧМТ [31]. Такий самий ефект має і блокатор ацетілхолінестерази галантамін, який, крім того, аллостерічно підсилював передачу сигналів N-холінорецепторів та зменшував дегенерацію ГАМК-ергічних нейронів у гіпокампі, що супроводжувалося покращенням когнітивних функцій [11]. На нашу думку, виражений позитивний ефект холіну альфосцерату може пояснюватися саме його модулюючим впливом на альфа7-холінорецептори, що попереджає кальцієві механізми пошкодження нервової тканини, які при ЧМТ є первинними та необоротними внаслідок активації кальпаїну, що призводе до апоптозу та нейродегенерації [9].

ВИСНОВКИ

1. При активації ЦХС у гострому періоді ЧМТ суттєво знижувалися летальність та неврологічний дефіцит, що супроводжувалося помірною активацією ГКАС.

2. Встановлено важливу роль ЦХС у реалізації посттравматичної стресової реакції нейроендокринної системи, а також можливість її фармакологічної корекції холіноміметиками центрального типу дії.

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ЗНАЧЕНИЕ АКТИВАЦИИ ЦЕНТРАЛЬНЫХ ХОЛИНЕРГИЧЕСКИХ СИСТЕМ ПРИ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМЕ

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Актуальность. Известно, что при черепно-мозговой травме (ЧМТ) активность центральных холинергических систем (ЦХС) угнетается, снижается высвобождение ацетилхолина и экспрессия холинергических рецепторов. Восстановление холинореактивности является актуальным направлением исследований и возможного терапевтического воздействия.

Цель – определить влияние активации ЦХС на летальность, неврологические нарушения и активность гипофизарно-кортикоадреналовой системы (ГКАС) в остром периоде ЧМТ.

Материал и методы. ЧМТ моделировали при свободном падении груза на фиксированную голову животного. Для активации ЦХС крысам до травмы вводили холина альфосцерат (глиатилин, 6 мг/кг), в контрольной группе вводили физиологический раствор. Неврологический дефицит оценивали по 100-балльной шкале Тодда. В плазме крови через 3, 24, 48 и 72 часа после травмы иммуноферментным методом определяли содержание адренокортикотропного гормона и кортикостерона (DSL; США). Результаты статистически обрабатывали с применением программ SPSS 11.0, MedStat, MedCalc.

Результаты. Летальность в контрольной группе составила 25,0%, в группе с активацией ЦХС летальных случаев не было ($p<0,05$). Неврологический дефицит в группе с активацией ЦХС был выражен значимо меньше по сравнению с контролем на всех сроках наблюдения. Содержание гормонов имело схожую динамику – достигало максимума через 24 часа и восстанавливалось через 72, однако при активации ЦХС прирост был в 1,4-1,5 раза меньше ($p<0,05$). Таким образом, использование холина альфосцерата для моделирования активности ЦХС приводило к снижению летальности и неврологического дефицита в остром периоде ЧМТ, что сопровождалось стабилизирующим влиянием на ГКАС.

Вывод. Установлена важная роль ЦХС в реализации посттравматической стрессовой реакции ГКАС, а также возможность ее фармакологической коррекции холином альфосцератом.

Ключевые слова: центральные холинергические системы; экспериментальная черепно-мозговая травма, холина альфосцерат.

THE IMPORTANCE OF CENTRAL CHOLINERGIC SYSTEMS ACTIVATION IN TRAUMATIC BRAIN INJURY

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Relevance. It is known that in traumatic brain injury (TBI), the activity of the central cholinergic systems (CChS) is inhibited, the release of acetylcholine and the expression of cholinergic receptors decrease. The restoration of cholinoreactivity is an urgent area of research and possible therapeutic direction.

Objective – to determine the effect of CChS activation on mortality, neurological disorders, and the activity of the pituitary-corticoadrenal system (PCAS) in the acute period of TBI.

Material and methods. TBI was simulated with a free load's fall on a fixed animal head. To activate the CChS, rats were injected with choline alfoscerate (gliatilin, 6 mg/kg) before injury, physiological saline was injected in the control group. Neurological deficit were assessed using the 100-point Todd scale. In blood plasma, 3, 24, 48 and 72 hours after injury, the content of adrenocorticotropic hormone and corticosterone was determined by the enzyme immunoassay method (DSL; USA). The results were statistically processed using the SPSS 11.0, MedStat, MedCalc software.

Results. Mortality in the control group was 25.0%, in the group with activation of the CChS there were no lethal cases ($p<0.05$). Neurological deficit in the group with CChS activation was significantly less pronounced compared to the control at all periods of observation. The hormone content had a similar dynamics: it reached a maximum after 24 hours and recovered after 72 hours, however, upon activation of the CChS, the increase was 1.4-1.5 times less ($p<0.05$). Thus, the use of choline alfoscerate for modeling the CChS activity led to the decrease in mortality and neurological deficit in the acute period of TBI, which was accompanied by a stabilizing PCAS function.

Conclusion. The important role of CChS in the implementation of post-traumatic stress reaction of PCAS, as well as the possibility of its pharmacological correction with choline alfoscerate, was established.

Key words: central cholinergic systems; experimental traumatic brain injury; choline alfoscerate.

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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 $h^{-1} \cdot kg^{-1}$ (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 $h^{-1} \cdot kg^{-1}$ (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 $h^{-1} \cdot kg^{-1}$ (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 $h^{-1} \cdot kg^{-1}$ (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 $h^{-1} \cdot kg^{-1}$ (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 $h^{-1} \cdot kg^{-1}$ (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≤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 continuos 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 знечуленням (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 білірубіну. 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: щури, 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: выяснить 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 внутрибрюшинно). 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 внутрибрюшинно). 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.

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THE ACID-BASE PROCESSES' CHANGES IN THE BODY OF WHITE RATS UNDER THE INFLUENCE OF NITROGEN-CONTAINING SURFACE-ACTIVE MATERIAL

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Relevance. Everyday contact of the population with surfactants (SAS) in drinking water poses the problem of timely and prompt substantiation of pre-nosological highly sensitive indicators of early manifestations of biological activity of detergents and operational control over the health of the population and the environment. But today the mechanisms of biotransformation, toxicodynamics, toxicokinetics and metabolic processes that underlie the formation of structural and metabolic disorders when exposed to a surfactant, taking into account possible long-term effects, have not yet been fully elucidated.

Objective: to investigate the effect of nitrogen-containing surfactants on redox processes in the body of experimental animals.

Materials and methods. The experiments were carried out on 620, and acute experiments on 128 white rats (weight 180-220 g). We used four ionic nitrogen-containing surfactants with specified technical and physicochemical characteristics: FOM 9, FOM 9-4, FOM 9-12 and FOM 9-20. Doses were chosen so as to determine the lethal effect in the lethal dose (LD) range from 0 to 100. The LD50 was calculated. The substances were introduced into the stomach in pure form using a metal probe. The animals were observed for up to 15 days. The time of death of the animals and the total amount of the introduced substance were recorded. The animals were subjected to postmortem examination. Redox processes were qualitatively assessed by the activity of enzymes: cholinesterase, cerulose plasmin, lactate dehydrogenase, malate dehydrogenase, succinate dehydrogenase, peroxidase, catalase, cytochrome oxidase, by the content of SH-groups in the blood, by the concentration of biogenic monoamines.

Results. Nitrogen-containing surfactants caused a change in peroxidase activity both upwards and downwards. In all cases, 1/1000 LD50 was inactive. On the 15th day of the experiment, neonol FOM 9-12 reduced the activity of the enzyme, and other substances did not affect it. By the end of the subacute experiment, neonol FOM 9-4 and neonol FOM 9-12 were reduced, and neonol FOM 9-20 increased peroxidase activity. A similar effect was on the activity of catalase: in all groups, except 1/1000 LD50, on day 30 there was a decrease in its activity. Cholinesterase activity increased. For the content of SH-groups in the blood on the 15th day there was a tendency to decrease, which turned into significant differences on the 30th day in 1/10 LD50. The effect of 1/100 and 1/1000 LD50 did not violate the content of SH-blood groups. A similar effect was on the content of glutathione in the blood. In a subacute experiment, in groups 1/10 and 1/100 LD50, the content of norepinephrine, tryptophan, serotonin in the liver increased and DOPA and dopamine decreased. The dynamics of adrenaline did not change. The content of dopamine and norepinephrine increased to a lesser extent in the brain; DOPA and adrenaline did not differ from the control; tryptophan increased only under the influence of FOM-9. 1/1000 LD50 did not affect the dynamics of the content of biogenic monoamines. The tested drugs have a similar effect on the body.

Conclusions. A more toxic substance in a subacute experiment is FOM-9. The severity of violations in the dynamics of monitoring the activity of enzymes has a close dose dependence. The effective dose is set at 1/10, the threshold – 1/100 and the inactive – 1/1000 LD50. Common features of the biological action of nitrogen-containing surfactants are the violation of redox processes, bioenergy, oxidative phosphorylation, which under appropriate conditions lead to the pathology of vital organs, functions and systems of the body.

Key words: nitrogen-containing surfactants, oxidation-reduction processes, biological action, dose dependence.

Relevance. The problem of protecting centralized surface sources of drinking water supply from pollution with surface-active substances (SAS) has acquired particular relevance today in Ukraine and requires scientific substantiation and the development of new, more stringent approaches to methods for assessing the sanitary and ecological situation in the basins of these reservoirs, as well as the introduction of effective ecological hygienic measures to protect both water sources and public health.

Everyday contact of the population with psychoactive substances poses the task of timely and operational substantiation of pre-nosological highly sensitive indicators of early manifestations of biological activity of detergents and operational monitoring of the health of the population and the environment for physicians and biologists. The solution of these issues requires a deep study of the mechanisms of biotransformation, toxicodynamics, toxicokinetics and metabolic processes that underlie the formation of structural and metabolic disorders when exposed to surfactants, taking into account possible long-term effects [6, 8].

Objective: to investigate the effect of nitrogen-containing surfactants on redox processes in the body of experimental animals.

MATERIALS AND METHODS

Four ionic nitrogen-containing surfactants with specified technical and physicochemical characteristics were used as research objects: FOM 9, FOM 9-4, FOM 9-12 and FOM 9-20 (FOM is the Mannich phenolic base).

In the experimental part of the work to obtain the required actual material, 620 white rats were used. 128 acute rats (weight 180-220 g) were used in acute experiments.

Experiments on white rats were performed by the method of Behrens-Schlosser [2]. Doses were chosen so as to determine the lethal effect in the range of LD0-LD100. LD50 calculations were performed according to Kerber, Behrens-Schlosser.

Substances were injected into the stomach in pure form using a metal probe. The animals were observed for up to 15 days. The time of death of animals and the total amount of the injected substance was registered. The results were evaluated on the basis of the average effective time of death of the animals [4]. Dead animals and survivors were subjected to pathological autopsy during these observation periods.

Qualitative evaluation of redox processes was studied by the activity of enzymes: ceruloplasmin, lactate dehydrogenase (LDH), malate dehydrogenase (MDG), succinate dehydrogenase (SDG), peroxidase, catalase, cytochrome oxidase and others [5]. To determine the activity of serum oxidase (ceruloplasmin), which directly fixes oxygen, used the method of H.A. Ravin in modification G.A. Babenka (1968) [4]. Cytochrome oxidase activity was determined by G.A. Gudilova and N.I. Sorokina (1968) by oxidation by cytochrome oxidase of reducing cytochrome C [24]. The activity of serum LDH was judged by the amount of pyruvic acid formed, which was determined colorimetrically using 2,4-dinitrophenylhydrazine [3]. The MDG of malic acid was determined by the Warburg test [7]. Determination of blood catalase was performed by Bach and Zubkova [7]. The content of SH-groups in the blood was detected by the method of ampermetric titration with silver nitrate, proposed by Kolthof and Harris, in the modification of V.V. Sokolovsky [9]. The concentration of biogenic monoamines was determined by the method of Y. Endo and Y. Ogura, for their binding was used carboxymethyl cellulose company «Reanal».

RESULTS AND DISCUSSION

All test substances after the end of the subacute experiment statistically significantly in 1/10 and 1/1000 LD50 reduced serum creatine phosphokinase activity, increased the activity of lactate dehydrogenase, asparagine and alanine aminotransferases, γ-glutamate transferase and Neonol FOM 9-20, neonol FOM 9-4 and FOM 9-12 reduced the activity of α-hydroxybutyrate dehydrogenase. In other cases, there was both an increase and decrease.

In groups of animals under the influence of nitrogen-containing surfactants in 1/10 and 1/100 LD50 there was an increase in the activity of cholinesterase (HE) in serum and acetylcholinesterase (AHE) – in the brain (Table 1). 1/1000 LD50 was inactive according to this indicator.

Cholinesterase is known to be found in the liver, blood plasma and other tissues. In many ways, it is an indicator of the functional activity of the liver and CNS. Therefore, the observed increase in the activity of this enzyme can be interpreted as the primary response of the liver to the action of nitrogen-containing surfactants and its participation in the formation of protective and adaptive mechanisms and the action of xenobiotics.

An important place in the anti-radical protection of the body belongs to peroxidase, which plays a leading role in the decomposition of peroxides and free radicals. Nitrogen-containing surfactants in the dynamics of observation caused a change in the activity of this enzyme both upwards and downwards. In all cases, 1/1000 LD50 was inactive (Table 2).

Thus, on the 15th day of the experiment, neonol FOM 9-12 reduced the activity of the enzyme, and the other substances did not affect it. By the end of the subacute experiment, neonol FOM 9-4 and neonol FOM 9-12 were

Table 1

Dynamics of XE and ACE activity in white rats in a subacute experiment (M±m), Δ pH/1 year

Substance	Dose, LD50	Observation period, days		
		HE (blood serum), pH/1 year		AHE (brain)
		15 days	30 days	30 days
Control		0,375±0,03	0,490±0,037	0,065±0,010 ↑
FOM-9	1/10	0,466±0,02 ↑	0,860±0,04 ↑	0,129±0,012 ↑
	1/100	0,443±0,03 ↑	0,754±0,03 ↑	0,140±0,014 ↑
Neonol FOM 9-4	1/10	0,526±0,03 ↑	0,931±0,14 ↑	0,960±0,009 ↑
	1/100	0,429±0,01 ↑	0,820±0,07 ↑	0,156±0,023 ↑
Neonol FOM 9-12	1/10	0,536±0,03 ↑	0,794±0,06 ↑	0,112±0,005 ↑
	1/100	0,487±0,02 ↑	0,916±0,08	0,136±0,090 ↑
Neonol FOM 9-20	1/10	0,475±0,02 ↑	1,183±0,05 ↑	0,113±0,005 ↑
	1/100	0,520±0,03 ↑	0,679±0,031 ↑	0,140±0,008 ↑

Note: ↑ - increase activity, P<0,05

Table 2

Dynamics of blood peroxidase activity (c) in a subacute experiment

Substance	Dose, LD50	Observation period, days			
		15 days		30 days	
		M±m	P	M±m	P
Control		80,83±5,83		52,50±2,14	
FOM-9	1/10	98,32±4,72	>0,05	44,73±3,28	>0,05
	1/100	96,15±6,13	>0,05	45,81±2,17	>0,05
Neonol FOM 9-4	1/10	67,40±3,15	>0,05	36,45±4,63 ↓	<0,05
	1/100	65,12±4,18	>0,05	37,29±2,85 ↓	<0,05
Neonol FOM 9-12	1/10	57,83±5,19 ↓	<0,05	40,26±3,17 ↓	<0,05
	1/100	68,74±4,60	>0,05	41,38±4,29 ↓	<0,05
Neonol FOM 9-20	1/10	80,55±2,46	>0,05	93,34±9,62 ↑	<0,05
	1/100	84,27±3,85	>0,05	95,82±8,30 ↑	<0,05

Note: ↑ – increase activity; ↓ – decrease activity

Table 3

Dynamics of blood catalase (C) activity in a subacute experiment

Substance	Dose, LD50	Observation period, days			
		15 days		30 days	
		M±m	P	M±m	P
Control		80,83±5,83		52,50±2,14	
FOM-9	1/10	98,32±4,72	>0,05	44,73±3,28	>0,05
	1/100	96,15±6,13	>0,05	45,81±2,17	>0,05
Neonol FOM 9-4	1/10	67,40±3,15	>0,05	36,45±4,63 ↓	<0,05
	1/100	65,12±4,18	>0,05	37,29±2,85 ↓	<0,05
Neonol FOM 9-12	1/10	57,83±5,19 ↓	<0,05	40,26±3,17 ↓	<0,05
	1/100	68,74±4,60	>0,05	41,38±4,29 ↓	<0,05
Neonol FOM 9-20	1/10	80,55±2,46	>0,05	93,34±9,62 ↑	<0,05
	1/100	84,27±3,85	>0,05	95,82±8,30 ↑	<0,05

Note: ↑ – increase activity; ↓ – decrease activity

Table 4

The content of the SH group (mg%) in the blood of white rats

Substance	Dose, LD50	Observation period, days			
		15 days		30 days	
		M±m	P	M±m	P
Control		82,57±2,84		84,71±3,50	
FOM-9	1/10	69,20±1,35	<0,05	62,17±2,11	<0,05
	1/100	76,35±4,26	>0,05	79,15±3,86	>0,05
Neonol FOM 9-4	1/10	78,52±3,64	>0,05	66,32±2,94	<0,05
	1/100	80,38±5,16	>0,05	88,57±3,25	>0,05
Neonol FOM 9-12	1/10	86,22±4,13	>0,05	64,25±3,17	<0,05
	1/100	80,35±2,97	>0,05	87,19±4,61	>0,05
Neonol FOM 9-20	1/10	85,43±2,15	>0,05	70,38±2,26	<0,05
	1/100	81,92±6,24	>0,05	89,63±4,35	>0,05

Table 5

The content of glutathione (mg%) in the blood of white rats

Substance	Dose, LD50	Observation period, days			
		15 days		30 days	
		M±m	P	M±m	P
Control		13,70±2,24		12,68±1,93	
FOM-9	1/10	12,10±3,26	<0,05	8,74±1,66	<0,05
	1/100	14,29±1,83	>0,05	14,72±2,25	>0,05
Neonol FOM 9-4	1/10	11,74±3,46	>0,05	7,96±2,16	<0,05
	1/100	12,15±1,92	>0,05	15,96±2,37	>0,05
Neonol FOM 9-12	1/10	11,79±2,78	>0,05	10,42±3,58	<0,05
	1/100	14,16±3,56	>0,05	14,13±2,74	>0,05
Neonol FOM 9-20	1/10	10,23±3,74	>0,05	112,82±3,19	<0,05
	1/100	15,48±1,87	>0,05	13,66±2,78	>0,05

reduced, and neonol FOM 9-20 increased peroxidase activity.

The studied nitrogen-containing surfactants had a similar effect on catalase activity (Table 3). In all groups of animals, except 1/1000 LD50, for 30 days there was a decrease in its activity. The detected changes in enzymatic activity may be associated with depletion of function as a result of the accumulation in the body of peroxides, hydroperoxides, free radicals.

It is known that surfactants, acting on the cell membrane, disrupt the structure of unsaturated fatty acids, which are sources of free radicals, and surfactants themselves, metabolized in the body, form peroxides, hydroperoxides, aldehydes, ketones. These are the sources to quench the consumption of this enzyme. It can be assumed that nitrogen-containing surfactants in 1/10 and 1/100 LD50 lead to the accumulation in the body of underoxidized products in the form of peroxides, hydroperoxides, aldehydes, free radicals, ketones and others. FOM-9 and neonol FOM 9-4 had a stronger effect on the state of the antioxidant system. Studies have shown that surfactants to some extent in the tested doses affect the content of SH-groups in the blood of white rats (Table 4).

As can be seen from the table above, on the 15th day of the experiment there was a tendency to decrease, which turns into significant differences on the 30th day of the experiment in 1/10 LD50. The effect of 1/100 and 1/1000 LD50 did not disrupt the dynamics of the content of SH-blood groups. Redox processes in tissues and organs are known to be maintained at a certain level by the ratio of sulfhydryl SH groups and disulfide SS groups in proteins and especially in enzyme proteins. The catalytic properties of many enzymes, such as β-amylase, carboxylase, cholinesterase, and others, as well as the processes of tissue respiration and detoxification of poisons, are associated with free SH groups. Sulfhydryl groups are the active principle of coenzyme A, which is involved in many processes of intermediate metabolism. Sulfur-containing enzymes lose catalytic activity when blocking SH groups of proteins.

Thus, the reduction of sulfhydryl groups under the influence of 1/10 LD50 nitrogen-containing surfactants may indicate a violation of redox processes in animals that have been seeded with this dose. Insignificant increase of SH-groups under the influence of 1/100 LD50 can be considered as a compensatory-adaptive reaction. The threshold, therefore, is 1/100 LD50.

Nitrogen-containing surfactants have a similar effect on the dynamics of the blood content of the tripeptide – glutathione and sulfhydryl groups (Table 5).

However, it should be noted that the severity of the shifts is somewhat weaker in relation to the effect of substances on blood glutathione. As can be seen from the table, on the 15th day there was a tendency to reduce it to 1/10 LD50 in all groups of animals. By the end of the subacute experiment, the test compounds FOM-9 and neonol FOM 9-4 reduced this value in the blood, 1/100 LD50 led to its increase, although it is not statistically significant that it should be considered as a protective and adaptive response of the body to toxic surfactants. threshold, and 1/10 LD50 – the current value.

In a subacute experiment in groups of animals exposed to nitrogen-containing surfactants 1/10 and 1/100 LD50, a change in the dynamics of biogenic monoamines and their precursors in the brain and liver was detected. Thus, in the liver there was an increase in noradrenaline, tryptophan, serotonin and a decrease in DOPA and dopamine. The dynamics of adrenaline did not change. In the brain, the changes were less pronounced and were characterized by an increase in dopamine and norepinephrine. Other indicators (DOPA, adrenaline) did not differ from the control. Tryptophan increased only under the influence of FOM-9. 1/1000 LD50 did not affect the dynamics of the content of biogenic monoamines and their precursors in the liver and brain of experimental animals.

The results of the studies confirm that the tested drugs have a similar effect on the body.

CONCLUSIONS

1 1. A more toxic substance in a subacute experiment is FOM-9.

2. The severity of violations in the dynamics of observation of enzyme activity has a close dose dependence. The effective dose is set at 1/10, the threshold - 1/100 and the inactive - 1/1000 LD50.

3. Common features of the biological action of nitrogen-containing surfactants are violations of redox processes, bioenergy, oxidative phosphorylation, which under appropriate conditions lead to pathology of vital organs, functions and systems of the body.

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ЗМІНИ ОКИСЛЮВАЛЬНО-ВІДНОВНИХ ПРОЦЕСІВ В ОРГАНІЗМІ БІЛИХ ЩУРІВ ПІД ВПЛИВОМ АЗОТВМІСНИХ ПОВЕРХНЕВО-АКТИВНИХ РЕЧОВИН

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Актуальність. Повсякденний контакт населення з поверхнево-активними речовинами (ПАР) у питній воді ставить задачу своєчасного і оперативного обґрунтування донозологічних високочутливих показників ранніх проявів біологічної активності детергентів і оперативного контролю за станом здоров'я населення і навколишнього середовища. Але сьогодні ще не до кінця з'ясовані механізми біотрансформації, токсикодинаміки, токсикокинетики і метаболічних процесів, що лежать в основі формування структурно-метаболічних порушень при дії на організм ПАР з урахуванням можливих віддалених ефектів.

Мета: дослідити вплив азотовмісних поверхнево-активних речовин на окислювально-відновні процеси в організмі експериментальних тварин.

Матеріали та методи. Досліди проведено на 620, а гострі досліди – на 128 білих щурах (маса 180-220 г). Використовували чотири іоногенних азотовмісних ПАР с заданими технічними та фізико-хімічними характеристиками: ФОМ 9, ФОМ 9-4, ФОМ 9-12 та ФОМ 9-20. Дози обирали так, щоб визначити летальний ефект в інтервалі ЛД0-ЛД100. Розраховували ЛД50. Речовини вводили в шлунок у чистому виді за допомогою металевого зонду. Спостерігали за тваринами до 15 днів. Реєстрували час загибелі тварин і сумарну кількість введеної речовини. Тварини підлягали патологоанатомічному розтину. Якісно оцінювали окислювально-відновлювані процеси за активністю ферментів: холінестерази, церулозплазміну, лактатдегідрогенази, малатдегідрогенази, сукцинатдегідрогенази, пероксидази, каталази, цитохромоксидази, за вмістом SH-груп у крові, за концентрацію біогенних моноамінів (адреналіну, норадреналіну, триптофану, серотоніну, ДОФА і дофаміну).

Результати. Азотовмісні ПАР викликали зміну активності пероксидази як у бік підвищення, так і зниження. У всіх випадках 1/1000 ЛД50 була недіючою. На 15 добу досліду неонол ФОМ 9-12 знижував активність ферменту, а решта речовин не чинили на нього впливу. До закінчення підгострого експерименту неонол ФОМ 9-4 і неонол ФОМ 9-12 знижували, а неонол ФОМ 9-20 підвищував активність пероксидази. Подібний вплив був і на активність каталази: у всіх групах, крім 1/1000 ЛД50, на 30 добу спостерігалося зниження її активності. Активність холінестерази підвищувалася. Для вмісту SH-груп в крові на 15 добу відзначалася тенденція до їх зниження, що переходила в достовірні відмінності на 30 добу в 1/10 ЛД50. Вплив 1/100 і 1/1000 ЛД50 не порушував вміст SH-груп крові. Подібний вплив був і на вміст у крові глутатіону. У підгострому досліді, у групах 1/10 і 1/100 ЛД50, в печінці збільшувався вміст норадреналіну, триптофану, серотоніну і знижувався ДОФА і дофаміну. Динаміка адреналіну не змінювалася. В головному мозку в меншій мірі збільшувався вміст дофаміну та норадреналіну; ДОФА і адреналін не відрізнялися від контролю; триптофан же підвищувався тільки під впливом ФОМ-9. 1/1000 ЛД50 не чинила впливу на динаміку вмісту біогенних моноамінів. Випробовувані препарати мають схожу дію на організм.

Висновки. Більш токсичною речовиною в підгострому досліді є ФОМ-9. Виразність порушень в динаміці спостереження активності ферментів має тісну дозову залежність. Діюча доза визначена на рівні 1/10, порогова – 1/100 і недіюча – 1/1000 ЛД50. Спільними особливостями біологічної дії азотовмісних поверхнево-активних речовин є порушення окислювально-відновних процесів, біоенергетики, окислювального фосфорилювання, які за відповідних умов призводять до патології життєво важливих органів, функцій і систем організму.

Ключові слова: азотовмісні поверхнево-активні речовини, окислювально-відновні процеси, біологічна дія, дозова залежність.

ИЗМЕНЕНИЕ ОКИСЛИТЕЛЬНО-ВОССТАНОВИТЕЛЬНЫХ ПРОЦЕССОВ В ОРГАНИЗМЕ БЕЛЫХ КРЫС ПОД ВЛИЯНИЕМ АЗОТСОДЕРЖАЩИХ ПОВЕРХНОСТНО-АКТИВНЫХ ВЕЩЕСТВ

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Актуальность. Повседневный контакт населения с поверхностно-активными веществами (ПАВ) в воде ставит задачу своевременного и оперативного обоснования донозологичних высокочувствительных показателей ранних проявлений биологической активности моющих средств и оперативного контроля за состоянием здоровья населения и окружающей среды. Но сегодня еще не до конца выяснены механизмы биотрансформации, токсикодинамики, токсикокинетики и метаболических процессов, лежащих в основе формирования структурно-метаболических нарушений при воздействии на организм ПАВ с учетом возможных отдаленных эффектов.

Цель: исследовать влияние азотсодержащих поверхностно-активных веществ на окислительно-восстановительные процессы в организме экспериментальных животных.

Материалы и методы. Опыты проведены на 620, а острые опыты – на 128 белых крысах (масса 180-220 г). Использовали четыре ионогенных азотсодержащих ПАВ с заданными техническими и физико-химическими характеристиками: ФОМ 9, ФОМ 9-4, ФОМ 9-12 и ФОМ 9-20. Дозы выбирали так, чтобы определить летальный эффект в интервале ЛД0-ЛД100. Рассчитывали ЛД50. Вещества вводили в желудок в чистом виде с помощью металлического зонда. Наблюдали за животными до 15 дней. Регистрировали время гибели животных и суммарное количество введенного вещества. Животные подлежали патологоанатомическому вскрытию. Качественно оценивали окислительно-восстановительные процессы по активности ферментов: холинэстеразы, церулозплазмину, лактатдегидрогеназы, малатдегидрогеназы, сукцинатдегидрогеназы, пероксидазы, каталазы, цитохромоксидазы, по содержанию SH-групп в крови, по концентрации биогенных моноаминов (адреналина, норадреналина, триптофана, серотонина, ДОФА и дофамина).

Результаты. Азотсодержащие ПАВ вызвали изменение активности пероксидазы как в сторону повышения, так и снижения. Во всех случаях 1/1000 ЛД50 была недействующей. На 15 сутки опыта неонол ФОМ 9-12 снижал активность фермента, а остальные вещества не оказывали на него влияния. До окончания подострого эксперимента неонол ФОМ 9-4 и неонол ФОМ 9-12 снижали, а неонол ФОМ 9-20 повышал активность пероксидазы. Подобное влияние было и на активность каталазы: во всех группах, кроме 1/1000 ЛД50, на 30 сутки наблюдалось снижение ее активности. Активность холинэстеразы повышалась. Для содержания SH-групп в крови на 15 сутки отмечалась тенденция к снижению, переходящая в достоверные различия на 30 сутки в 1/10 ЛД50. Влияние 1/100 и 1/1000 ЛД50 не нарушало содержание SH-групп крови. Подобное влияние было и на содержание в крови глутатиона. В подостром опыте, в группах 1/10 и 1/100 ЛД50, в печени увеличивалось содержание норадреналина, триптофана, серотонина и снижалось – ДОФА и дофамина. Динамика адреналина не менялась. В головном мозге в меньшей степени увеличивалось содержание дофамина и норадреналина; ДОФА и адреналин не отличались от контроля; триптофан же повышался только под влиянием ФОМ 9. 1/1000 ЛД50 не оказывала влияния на динамику содержания биогенных моноаминов. Испытуемые препараты обладают схожим действием на организм.

Выводы. Более токсичным веществом в подостром опыте есть ФОМ 9. Выраженность нарушений в динамике наблюдения активности ферментов имеет тесную дозовую зависимость. Действующая доза определена на уровне 1/10, пороговая – 1/100 и недействующая – 1/1000 ЛД50. Общими особенностями биологического действия азотсодержащих поверхностно-активных веществ является нарушение окислительно-восстановительных процессов, биоэнергетики, окислительного фосфорилирования, которые при соответствующих условиях приводят к патологии жизненно важных органов, функций и систем организма.

Ключевые слова: азотсодержащие поверхностно-активные вещества, окислительно-восстановительные процессы, биологическое действие, дозовая зависимость.

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CYP2E1-DEPENDENT VARIATIONS IN HEPATOCYTES DAMAGE DURING TREATMENT OF TUBERCULOSIS

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Relevance. Investigation of polymorphism in a locus of CYP2E1 as the prognostic factor of drug induced hepatotoxicity at anti-TB therapy is significant due to the influence of CYP2E1 on drug metabolism.

The objective of investigation is to analyze association of rs2070676 CYP2E1 gene polymorphism with drug-induced hepatotoxicity by means of the clinical-laboratory values of serum transaminases at anti-TB treatment.

Materials and methods. The study involved 47 patients with a drug susceptible tuberculosis first time discovered. 58 healthy volunteers comprised a control group. Laboratory indices were determined in venous blood three times: before the treatment as baseline; in 2 months of intensive therapy (isoniazid, rifampicin, ethambutol, pyrazinamide), then in 4 months of maintenance therapy (isoniazid, rifampicin). Serum activities of enzymes ALT, AST and GGT were measured by standard algorithm on automatic analyzer BS-300. Analysis of rs2070676 polymorphism of CYP2E1 gene was performed by polymerase chain reaction using standard PureLink® Genomic DNA Kit for Purification of Genomic DNA; Manufacturer of INVITROGEN (USA). For statistical processing, IBM SPSS Statistics 23 was applied.

Results. Investigation of serum ALT and AST in patients with major genotype CYP2E1 (C/C) showed the lower baseline ALT and AST levels comparing to the control group, which might be caused by suppression of hepatocytes functions at development of disease. Anti-TB treatment caused an increase in ALT and AST levels comparing to the baseline in patients with major CYP2E1 (C/C) genotype. In the group with C/G polymorphism the baseline ALT level didn't differ much from the baseline of the control group; it showed a decrease after intensive therapy and returned back to initial level at maintenance therapy. This might be related to the certain protective property of CYP2E1 gene polymorphism. The AST level was increased after intensive therapy (in smaller extend than for the patients with major C/C genotype) and remained on the same level at maintenance therapy. Study of GGT showed a gradual increase regardless of genotype.

Conclusion. According to the data of experiment the status of hepatocytes in patients with tuberculosis at baseline and during treatment was different depending on CYP2E1 genotype. The results of experiment indicate that CYP2E1 gene polymorphism has a certain protecting role. It reduces the level of drug metabolites and hepatotoxicity which cause the mitochondrial dysfunction.

Key words: transaminase, antituberculosis therapy, hepatotoxicity, mitochondrial dysfunction, polymorphism

Relevance. Tuberculosis is one of the major social problems nowadays which concerns all countries in the world including Ukraine. Modern antituberculosis treatment requires to use the long-term chemotherapy (6-20 month depending on the type and severity of disease). Despite the high efficiency, the first line medications (isoniazid, rifampicin, pyrazinamide, ethambutol) have noticeable adverse effects, the most common of which is hepatotoxicity [1, 2]. The mechanisms of drug-induced hepatotoxicity development, including isoniazid-associated, are related to the toxicity of drug metabolites [3-5] which are formed with involvement of cytochrome P-450 enzymes [6]. The risk of hepatotoxicity development depends on polymorphism of xenobiotic detoxification genes. Mononucleotide polymorphisms have an influence on the activity of cytochrome P-450 enzymes [7] which specify the pathways of drug metabolism.

The metabolic inactivation of drugs such as isoniazid and rifampicin take place in presence of enzyme CYP2E1, the component of cytochrome P 450. The polymorphism of CYP2E1 (rs2070676) gene is related to the replacement of Cytosine (C) with Guanine (G) in tenth chromosome that may change the enzyme activity. The large number of CYP2E1 gene mutations are described [], however its influence on the activity of enzyme CYP2E1 is not fully studied. This makes it important to study the polymorphism in a locus of CYP2E1 gene as a prognostic factor of drug induced hepatotoxicity at antituberculosis treatment.

The objective of the study is to analyze the association of rs2070676 CYP2E1 gene polymorphism in tuberculosis patients with drug -induced hepatotoxicity by means of the clinical-laboratory values of serum transaminases (ALT, AST, GGT) at the time of anti-TB treatment.

MATERIALS AND METHODS

The study involved 131 persons. Among them were 73 patients of a specialized anti-tuberculosis dispensary with a drug susceptible tuberculosis first time discovered. 58 healthy volunteers comprised a control group.

Examination and treatment were carried with the written mandatary consent of patient to participate in the trial (protocol № 128, 23.12.2019, bioethics commission of Bogomolets National medical university).

The patients were treated with a standard regimen during 6 months: 2 months of intensive therapy (IT – isoniazid, rifampicin, ethambutol, pyrazinamide), then 4 months of maintenance therapy (MT - isoniazid, – rifampicin). Laboratory indices were measured in venous blood three times: first time – before the treatment as baseline; second time – in 2 months of intensive therapy, third time – in 4 months of maintenance therapy. Only 47 patients were monitored in this way, others were excluded from the study for different reasons. The median age in the group of patients was 42,7 ± 2,2 year; it was comparable with the median age of the control group. The group of patients contained a larger number of men in comparison to the control group but the difference was insignificant.

Serum activities of enzymes ALT, AST and GGT were measured by standard algorithm with automatic analyzer BS-300. Analysis of rs2070676 polymorphism of CYP2E1 gene was performed by polymerase chain reaction using standard PureLink® Genomic DNA Kit for Purification of Genomic DNA; Manufacturer of INVITROGEN (USA). For statistical processing, IBM SPSS Statistics 23 was applied. The data in the groups were compared by means of univariate analysis with non-parametric Kruskal-Wallis test. The diagrams were presented with a confidence interval (95% confidence interval).

Table 1

Analysis of distribution of alleles and genes of CYP2E1 in the control group and in a group of TB patients, % (number of persons in a group)

Genetic marker/ group	Control group, n = 58	TB patients, n = 73
C/C	74% (43)	75% (55)
C/G	26% (15)	25% (18)
G/G	0	0
C	87% (101)	87,6 % (128)
G	13% (15)	12,4% (18)

RESULTS AND DISCUSSION

The first step of research was an analysis of gene CYP2E1 genotype distribution (table 1). The percentage of gene polymorphism carriers was similar in the group of TB patients and in the control group; it indicates that there is no association of CYP2E1 gene polymorphism with development of tuberculosis. Major C/C genotype was found in ¾ cases in both groups, heterozygous C/G polymorphism was found in ¼ cases. Homozygous mutation G/G was not found.

Alanine aminotransferase (ALT) is an endogenic enzyme of transferase group widely used in medical practice as the marker in laboratory diagnostics of liver damage. Investigation of serum transaminase activity showed the median value of ALT in the control group equal to 0,47 mkkat (27.6 U/l). It corresponds well to the reference value of < 41 U/l for men and < 31 U/l for women. The level of serum ALT in the group of TB patients before treatment was 0.17 mkkat, 2.5 times lower than in the control group (fig. 1A).

After treatment by the first line medications which are potentially hepatotoxic the level of serum ALT was elevated 2 times (it is commonly interpreted as inflammation) but its absolute value remained within the range of reference values (0.37 mkkat) and was still

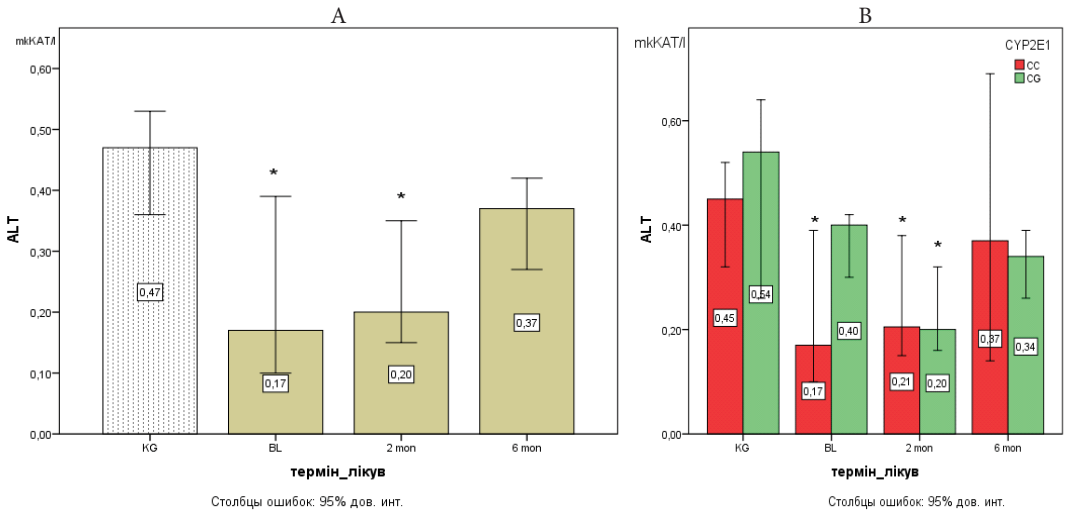

Fig. 1. Serum ALT levels in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

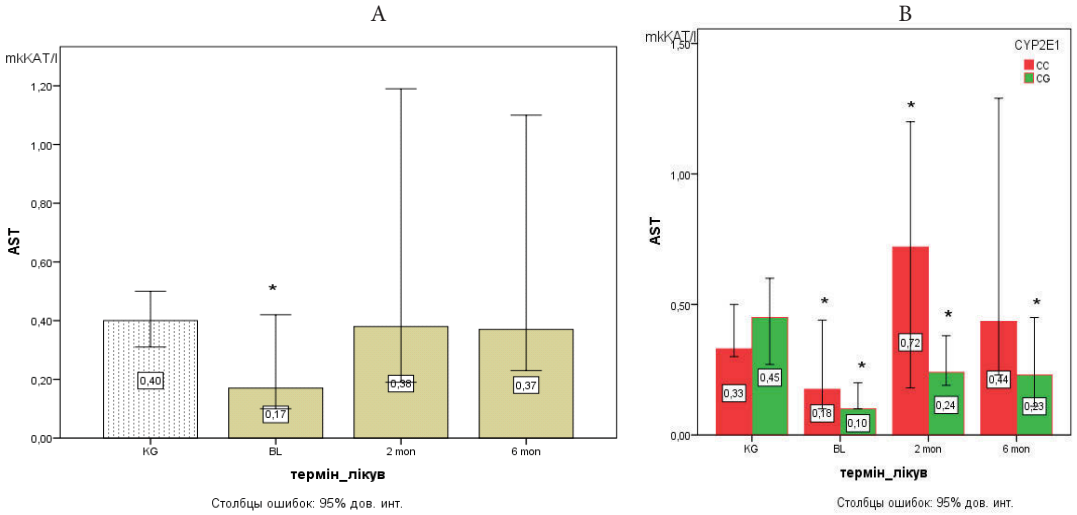

Fig. 2. Serum AST levels in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

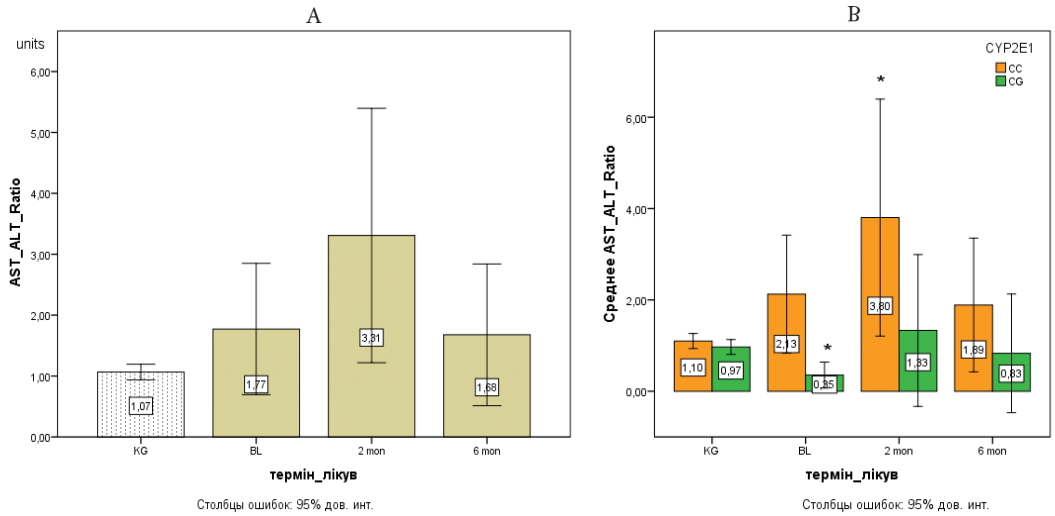

Fig. 3. De Ritis ratio (AST/ALT ratio) in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

lower than in the control group of healthy volunteers. In such case the comparison of ALT levels measured for the group of TB patients with the value measured for the control group of healthy volunteers looks unreasonable because the risk of misinterpretation.

Antituberculosis treatment increased the ALT level in the group of TB patients. After 6 months of treatment (intensive and maintenance therapy) the ALT level was 2 times higher than the baseline, that indicates the development of hepatocytes inflammation. Such response to the therapy was shown only by the carriers of major C/C genotype (fig. 1B).

The level of aspartate aminotransferase (AST) is an important biochemical criteria of hepatocytes status: increased serum AST indicates the larger damage of tissue due to the larger content of mitochondrial AST in a cell. The baseline AST in the group of TB patients was much lower comparing to the control group (fig. 2A). After 2 months of intensive therapy it became 2 times higher (but still lower than in the control group); at the time of maintenance therapy it remained on the same level. Thus, comparison of level of serum AST in the group of TB patients with the control group of healthy volunteers also looks unreasonable.

The AST level of patients with major C/C genotype demonstrated large increase in the stage of intensive therapy (4 times higher than the baseline). It is typical for the mechanism of hepatotoxicity development related to the processes in mitochondria. During maintenance therapy the gradual decrease of AST was observed. In the

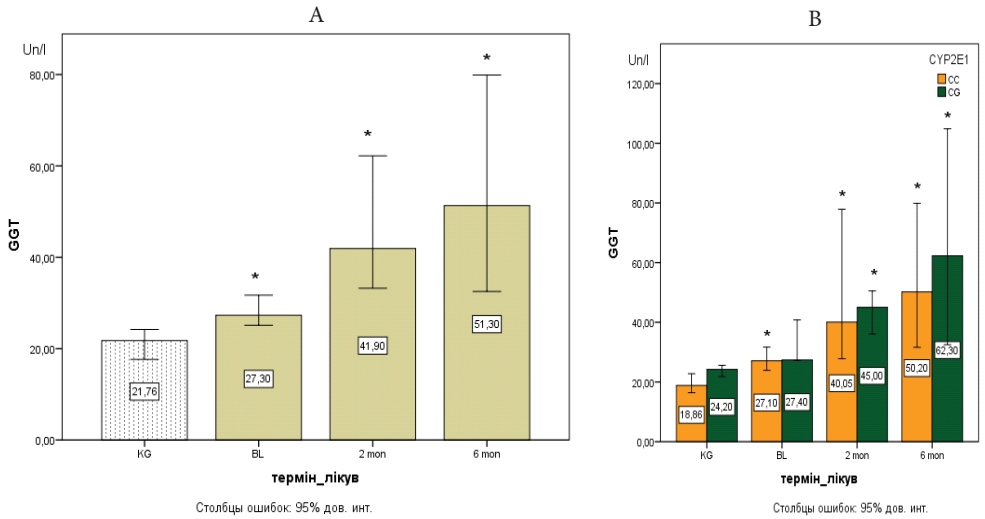

Fig. 4. Serum GGT levels in the control group and group of TB patients: baseline; in 2 months of intensive therapy; after 6 months of therapy. A – the overall group of patients; B – depending on CYP2E1 genotype. * P <0,05 compared to the corresponding category of the control group

group of carriers of C/G genotype the AST level became 2 times higher after intensive therapy; its value remained the same during maintenance therapy.

Study of De Ritis ratio in the group of TB patients showed its increase almost 2 times after intensive therapy (fig. 3A). Maintenance therapy returned the ratio back to the normal value (1,33±0,42). The sharp increase of De Ritis ratio during the stage of intensive therapy is typical for the cell necrosis which cause a release of cytosolic and mitochondrial AST into the serum. Analysis of De Ritis ratio for the carriers of major C/C genotype showed an increased level before the treatment and after intensive therapy which was getting back almost to the normal level at maintenance therapy. The carriers of C/G polymorphism showed the abnormally low baseline De Ritis ratio, which is more typical for inflammation. The gradual increase of De Ritis ratio almost to the normal level was observed during treatment (fig. 3B). This demonstrates the difference in the mechanisms of liver damage depending on the genotype and indicates the certain protecting role of CYP2E1 gene polymorphism.

Gamma-glutamyl transferase (GGT) is used as the laboratory marker of drug intoxication. The baseline GGT in the group of TB patients was a slightly higher than in the control group (fig. 4A). Anti-TB treatment caused the graduate increase of enzyme activity. After completing the treatment, the level of GGT was 2 times higher than the baseline. Genotype didn't affect the overall tendency, the elevation of GGT was observed regardless to the genotype of patients (fig. 4B).

There are numerous studies considering drug-induced hepatotoxicity at anti-TB treatment however just in some of it the baseline levels of biochemical markers measured for TB patients were compared with the corresponding values of healthy persons. The large deviations of baseline ALT in patients (without co-diseases) were not observed [9, 10] or it was reported the moderate increase of ALT associated with the larger risk of hepatotoxicity development [11]. An exception is the study [12], where it was mentioned a low baseline ALT (7.5±3.5 U/l) which corresponds well with our data.

The factors affecting ALT and AST levels are age [13] and gender. In our study the median age and gender distributions in the group of TB patients were comparable with those in the control group. Transaminase level also correlates with the body mass index (BMI) and lean mass index (LMS) [14, 15], the larger BMI is associated with larger ALT and AST. It was also reported that elevated ALT can be associated with alterations in glucose and lipid metabolism: reduced insulin sensitivity and glucose tolerance, increased fatty acids and triglycerides content [16]. Since in this study the BMI of TB patients was not taken into consideration, we cannot estimate its effect on baseline ALT level.

The low baseline level of transaminases in the group of TB patients might be related to the changes in fatty acid profile of hepatocyte membrane caused by development of tuberculosis. In detailed review [17] it was generalized that development of tuberculosis is accompanied by disorders of lipid metabolism: increased LDL, decreased HDL, changed ratio of free to esterified cholesterol. Similar observations were made by the authors of [18] which noted decreased free cholesterol, HDL, albumin and free fatty acids in TB patients. Disorders of lipid metabolism, its influence on the composition of lipoproteins and phospholipid profile of cell membranes worth the further study because the previous were mostly focused on the other aspects of the problem: on investigation of metabolism, transport and functions of lipids in mycobacteria cell wall, on the mechanisms of cholesterol and fatty acid utilization [19, 20].

We suppose that the low baseline level of ALT and AST observed in the group of TB patients might be explained by suppression of hepatocyte functions at disorder of lipid metabolism, although this question requires further study.

According to the results of experiment the carriers of C/G polymorphism had higher baseline ALT which didn't differ much from ALT level of the control group. Intensive therapy reduced the enzyme activity 2 times; maintenance therapy returned it at initial level. It might indicate that CYP2E1 heterozygous mutation provides the lower hepatocytes damage and associates with better regenerative ability.

The AST level of the carriers of major genotype was sharply increased after therapy that shows the high response of hepatocytes to the toxicity of first-line antituberculosis drugs. The carriers of C/G polymorphism demonstrated the smaller increase of AST comparing to the carriers of major allele. It might be assumed that the small variations of transaminase levels indicate the less intensive damage of mitochondria in the cell. The presence of gene polymorphism can be regarded as a protecting factor which provides the less intensive development of mitochondrial dysfunction.

Thus, the low baseline level of ALT in TB patients might be caused by suppression of hepatocyte functions at disorder of lipid metabolism. The use of transaminase values measured for healthy volunteers as baseline may mask the manifestation of hepatotoxicity development in TB patients. The mechanisms of hepatocytes damage before the treatment and during therapy were different depending on the gene CYP2E1 genotype. The heterozygous mutation contributed to the smaller hepatocytes damage at anti-TB treatment.

CONCLUSIONS

Distribution of gene CYP2E1 polymorphism in the group of healthy volunteers and in the group of TB patients were similar; it indicates that there is no association of CYP2E1 gene polymorphism with development of tuberculosis. Every fourth person had heterozygous polymorphism C/G. Homozygous mutation G/G was not found.

According to the experimental data the risk of drug-induced hepatotoxicity development was higher among the carriers of major C/C genotype. The patients with heterozygous gene CYP2E1 C/G polymorphism had lower extend of hepatocytes damage.

CYP2E1 gene polymorphism probably carries a certain protecting role: it reduces the level of drug metabolites and hepatotoxicity which cause the mitochondrial dysfunction.

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CYP2E1-ЗАЛЕЖНІ ВІДМІННОСТІ УШКОДЖЕННЯ ГЕПАТОЦИТІВ ПІД ЧАС ЛІКУВАННЯ ТУБЕРКУЛЬОЗУ

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Актуальність. Дослідження поліморфізму локусу CYP2E1, як прогностичного фактору розвитку гепатотоксичних реакцій під час протитуберкульозної терапії є актуальним через значний вплив CYP2E1 на метаболізм лікарських засобів.

Метою дослідження був аналіз асоціації поліморфізму rs2070676 гену CYP2E1 у хворих на туберкульоз із розвитком гепатотоксичності за клініко-лабораторними показниками трансаміназ крові на фоні протитуберкульозної терапії.

Матеріали та методи. В дослідженні приймали участь 47 пацієнтів з чутливою формою туберкульозу вперше виявлені. Контрольну групу порівняння складали 58 здорових добровольців. Лабораторні показники визначали в венозній крові: до початку лікування як базовий рівень; через 2 місяця інтенсивної терапії; через 4 місяця підтримуючої терапії. Активність ферментів АЛТ, АСТ та ГГТ в сироватці крові визначали за стандартними методиками на автоматичному аналізаторі BS-300. Аналіз поліморфізму rs2070676 гена CYP2E1 проводили методом полімеразної ланцюгової реакції з використанням стандартних реактивів «PureLink® Genomic DNA Kit For Purification of Genomic DNA»; виробник INVITROGEN (США). Для статистичної обробки використовували пакет IBM SPSS Statistics 23.

Результати. Вивчення сироваткової активності ферментів АЛТ та АСТ у хворих на туберкульоз показало зниження базового рівня АЛТ та АСТ відповідно до рівня контрольної групи, що може бути пов'язано з пригніченням функцій гепатоцитів під час розвитку захворювання. У динаміці лікування пацієнтів носіїв мажорного генотипу CYP2E1 (C/C) спостерігалося збільшення активності АЛТ та АСТ відповідно до базового рівня. У носіїв поліморфізму C/G базова активність ферменту АЛТ мало відрізнялась від аналогічного показника контрольної групи та демонструвала помітне зниження в ході інтенсивної терапії і відновлення до базового рівня на стадії підтримуючої терапії, що може свідчити про певні протекторні властивості поліморфізму гену CYP2E1. Рівень активності АСТ у носіїв поліморфізму збільшувався на стадії інтенсивної терапії, але не так значно, як для

носіїв мажорного генотипу, та подалі залишався незмінним. Дослідження рівня ГГТ – показало поступове підвищення рівня ферменту незалежно від генотипу.

Висновок. За даними дослідження функціональний стан гепатоцитів у хворих на ТБ відрізнявся, як на базовому рівні, так і у відповідь на терапію, в залежності від генотипу гену CYP2E1. Поліморфізм гену CYP2E1 виконує певну протекторну роль, зменшує кількість метаболітів протитуберкульозних ліків і гепатотоксичність, яка реалізується за рахунок мітохондріальної дисфункції.

Ключові слова: трансамінази, протитуберкульозна терапія, гепатотоксичність, мітохондріальна дисфункція, поліморфізм

CYP2E1-ЗАВИСИМЫЕ ОТЛИЧИЯ ПОВРЕЖДЕНИЯ ГЕПАТОЦИТОВ ПРИ ЛЕЧЕНИИ ТУБЕРКУЛЕЗА

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Актуальность. Исследование полиморфизма локуса CYP2E1, как прогностического фактора развития гепатотоксических реакций при антитуберкулезной терапии, является актуальным вследствие значительного влияния активности CYP2E1 на метаболизм лекарственных препаратов.

Целью исследования был анализ ассоциации полиморфизма rs2070676 гена CYP2E1 у больных туберкулезом с развитием гепатотоксичности по клинико-лабораторными показателям трансаминаз крови на фоне противотуберкулезной терапии.

Материалы и методы. В исследовании принимали участие 47 пациентов с чувствительной формой туберкулеза впервые выявленные. Контрольная группа сравнения включала 58 здоровых добровольцев. Лабораторные показатели определяли в венозной крови: до начала лечения как базовый уровень, через 2 месяца интенсивной терапии, через 4 месяца после поддерживающей терапии. Активность ферментов АЛТ, АСТ и ГГТ в сыворотке крови определяли по стандартным методикам на автоматическом анализаторе BS-300. Анализ полиморфизма rs2070676 гена CYP2E1 проведен методом полимеразной цепной реакции с использованием стандартных реактивов «PureLink® Genomic DNA Kit For Purification of Genomic DNA»; производитель INVITROGEN (США). Для статистической обработки использовали пакет IBM SPSS Statistics 23.

Результаты. Изучение сывороточной активности ферментов АЛТ и АСТ у пациентов с туберкулезом показало снижение базового уровня АЛТ и АСТ по сравнению с контрольной группой, что может быть связано с угнетением функций гепатоцитов при развитии заболевания.

В процессе лечения у пациентов носителей мажорного генотипа CYP2E1 (C/C) наблюдалось увеличение активности АЛТ и АСТ сравнению с базовым уровнем на фоне антитуберкулёзной терапии. У носителей полиморфизма C/G базовая активность фермента АЛТ мало отличалась от аналогичного показателя контрольной группы; демонстрировала заметное снижение в ходе интенсивной терапии и восстановление до базового уровня на стадии поддерживающей терапии, что может указывать на определенные протекторные свойства полиморфизма гена CYP2E1. Уровень активности АСТ увеличивался на стадии интенсивной терапии, но не так сильно, как для носителей мажорного генотипа, и дальше оставался неизменным. Исследование уровня ГГТ – показало постепенное повышение уровня фермента независимо от генотипа.

Выводы. Согласно результатам исследования, функциональное состояние гепатоцитов у пациентов с туберкулезом отличалось как до начала лечения, так в ответ на терапию в зависимости от генотипа гену CYP2E1. Полиморфизм гена CYP2E1 играет определенную протекторную роль, снижает количество метаболитов противотуберкулезных лекарственных препаратов и гепатотоксичность, которая реализуется за счет митохондриальной дисфункции.

Ключевые слова: трансаминазы, противотуберкулезная терапия, гепатотоксичность, митохондриальная дисфункция, полиморфизм

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FEATURES OF DYSLIPOPROTEINEMIA IN TYPE 2 DIABETES MELLITUS PATIENTS WITH PRIOR MYOCARDIAL INFARCTION

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Relevance. In diabetes mellitus (DM), atherosclerotic plaques contain more fat, are more inflammatory and show a higher risk of thrombus formation than in individuals without diabetes. One of the significant factors in the development and progression of atherosclerosis in these patients is atherogenic dyslipidemia, which includes a wide range of disorders and often precedes the onset of diabetes for several years. Therefore, it is relevant to study the features of dyslipidemia in patients with diabetes after myocardial infarction (MI).

Objective: to study changes in blood lipid spectrum parameters, including Apolipoproteins (Apo A-1, Apo B) and lipoprotein (a), in postinfarction patients with type 2 DM.

Materials and methods. 119 patients (77 men and 42 women; mean age 61.09 ± 0.92 years) were examined, of which 42 were patients with coronary heart disease (CHD) who suffered from MI and type 2 diabetes (main group), 39 patients with a history of MI without concomitant diabetes (comparison group I) and 38 patients with type 2 diabetes without MI (comparison group II). The control group consisted of 30 healthy individuals, comparable in age and sex. Total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDLC) were determined in venous serum by enzymatic colorimetric method. According to the formulas, the level of cholesterol in very low density lipoproteins (VLDLC) was calculated; cholesterol in low-density lipoprotein (LDLC), coefficient of atherogenicity (CA). The level of lipoprotein (a) – LP (a), Apo A-1 and Apo B was determined by immunoturbidimetry. Blood sampling in patients was performed on an empty stomach.

Results. In the main group, significantly higher rates of TC, TG, LDLC, VLDLC, AF, Apo B and the ratio of Apo B/Apo A-1, compared with non-diabetic postinfarction patients. At the same time, there was a significantly lower concentration of HDLC, Apo A-1 and LP (a) – in patients with a history of diabetes mellitus. When comparing the indicators of patients in the main group with patients with isolated type 2 diabetes, there were significantly higher levels of LDL cholesterol and CA, as well as significantly lower concentrations of HDL cholesterol and apo A-1 in patients of the main group. The analysis of lipid metabolism in the comparison groups revealed a difference in the level of TG, LDL cholesterol and Apo B, which have higher levels in patients with isolated type 2 diabetes, and the level of LP (a) – significantly higher in postinfarction patients, in contrast to diabetics. The results indicate deeper disorders of lipid metabolism in post-infarction patients with diabetes than in non-diabetic post-infarction patients, which may be due to insulin resistance, hyperinsulinemia and hyperglycemia.

Conclusions. Dyslipoproteinemia in postinfarction patients with type 2 diabetes is characterized by a decrease in the content of antiatherogenic HDL cholesterol and its protein Apo A-1, moderate hypertriglyceridemia, increased levels of LDL cholesterol, VLDL cholesterol and Apo B, which causes higher values of cholesterol and increases AF. Elevations in lipid profile parameters such as TG, LDL cholesterol, and Apo B are more associated with diabetes, while higher concentrations of LP (a) are characteristic of postinfarction non-diabetic patients.

Key words: type 2 diabetes mellitus, postinfarction cardiosclerosis, dyslipoproteinemia.

Relevance. The population of patients with type 2 diabetes mellitus (DM) is growing steadily, doubling every ten years [6]. The risk of developing coronary heart disease (CHD) in type 2 diabetes is 2-3 times higher in male patients and 3-7 times higher in women [5]. Patients with type 2 diabetes have a 2-4 times higher risk of dying from coronary heart disease than non-diabetic patients [1].

Atherosclerosis, which is the morphological basis of coronary pathology, develops in patients with type 2 diabetes 10-15 years earlier than in the general population, progresses rapidly and more often leads to complications [3, 14]. It is among these patients that the risk of developing myocardial infarction (MI) is 3-5 times higher, depending on gender, higher than in the non-diabetic population [2]. It is among patients with type 2 diabetes mortality during the first year after MI is 15-34%, reaching 45% in the next 5 years, which is twice as high as in the general population. Despite significant advances in the treatment of coronary heart disease and its consequences, patients with type 2 diabetes remain the most vulnerable group, as the reduction in mortality among them is insignificant [15].

Such disappointing prognosis for patients with type 2 diabetes is associated primarily with the accelerated development of atherosclerosis of large subepicardial vessels and its rapid progression [1]. The results of studies have shown that in diabetes atherosclerotic plaques contain more fat, are more inflammatory and show a higher risk of thrombosis than in people without diabetes [17]. One of the important factors in the development and progression of atherosclerosis in these patients is atherogenic dyslipidemia, which includes a wide range

of disorders and often precedes the onset of diabetes for several years [8].

Therefore, based on these data, we decided to investigate the features of dyslipidemia in patients with type 2 diabetes who suffered MI.

Objective: to study changes in blood lipid spectrum parameters, including Apolipoproteins (Apo A-1, Apo B) and lipoprotein (a), in postinfarction patients with type 2 DM.

MATERIALS AND METHODS

119 patients (77 men and 42 women, mean age of patients – 61.09 ± 0.92 years) were examined, of which 42 were patients with coronary heart disease who had MI and had type 2 diabetes (main group), 39 patients with History of MI without concomitant diabetes (comparison group I) and 38 patients with type 2 diabetes without MI (comparison group II). The control group consisted of 30 healthy individuals, comparable in age and sex. The general clinical characteristics of the examined patients are given in table 1.

All patients included in the study were tested for total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDLC) in the serum of venous blood by enzymatic colorimetric method using reagent kits «Human» (2000 Germany) bio (Germany, 2000), the results were expressed in mmol/l. The level of cholesterol in very low density lipoproteins (VLDLC) was calculated by the formula: TG×0.45 (mmol/l); cholesterol in low-density lipoprotein (LDLC) was calculated by the formula of Friedwald W.T. [12]: LDLC = TC - HDLC - VLDLC. The coefficient of atherogenicity (CA) was calculated according to the generally accepted formula [7]: CA = (HDL - HDLC)/ HDLC. The level of lipoprotein (a) – LP (a), Apo A-1 and Apo B was determined by immunoturbidimetry using the test system Roshe Diagnostics (Switzerland) on a Cobas 6000 analyzer (Switzerland). Units of measurement for LP (a) – mg/dl, and for Apo A-1 and Apo-B – g/l. Blood sampling in patients was performed on an empty stomach (last meal – more than 10 hours before blood sampling).

The research results are processed using the methods of variation statistics. Significance of differences when comparing the mean values was determined using Student's t-test (p). The difference was considered significant at $p<0.05$. The values of the studied indicators are presented in the form of M ± m, where M is the arithmetic mean, m is the standard error.

RESULTS AND DISCUSSION

The analysis of the obtained data in the main group of patients revealed significantly higher rates of TC

Table 1

General clinical characteristics of the examined patients

Indicator		Main group (n=42)	Isolated coronary heart disease: postinfarction cardiosclerosis (n=39)	Isolated type 2 diabetes mellitus (n=38)
Age, M±m years		61,66±1,78	61,17±1,08	60,04±1,16
Gender, n (%)	male	27 (64,3%)	26 (66,7%)	24 (63,2%)
	female	15 (35,7%)	13 (33,3%)	14 (36,8%)
Prescription of IM, M±m years		4,93±0,38	5,28±0,55	-
Prescription of DM, M±m years		8,34±0,67	-	7,66±0,71

Note: the difference between the groups is statistically insignificant (p>0,05).

Table 2

Indicators of lipid metabolism in patients with CHD who underwent MI and patients with type 2 DM in comparison with patients with MI without DM and patients with history of type 2 DM without MI (M ± m)

Indicator	Main group (n=42)	Isolated coronary heart disease: postinfarction cardiosclerosis (n=39)	Isolated type 2 diabetes mellitus (n=38)
TC, mmol/l	$5,99±0,29^{\Delta\Delta\Delta}$	4,92±0,20	5,32±0,22
TG, mmol/l	$2,76±0,28^{\Delta\Delta\Delta}$	$1,43±0,15^{\#\#\#}$	2,57±0,28
HDLC, mmol/l	$0,93±0,04^{\Delta\Delta}$**	1,13±0,06	1,07±0,04
LDLC, mmol/l	$3,81±0,27^{\Delta}$*	3,13±0,20	3,07±0,19
VLDLC, mmol/l	$1,24±0,13^{\Delta}$	$0,64±0,07^{\#\#\#}$	1,16±0,12
CA	$5,57±0,36^{\Delta\Delta\Delta}$***	3,62±0,33	4,05±0,27
Apo A-1, g/l	$1,29±0,05^{\Delta}$*	1,42±0,03	1,40±0,03
Apo B, g/l	$1,24±0,08^{\Delta}$	$1,06±0,04^{\#}$	1,23±0,08
Apo B/Apo A-1	$0,94±0,06^{\Delta\Delta\Delta}$	0,72±0,03	0,81±0,06
LP (a), mg/dl	$23,29±4,28^{\Delta}$	$42,17±7,31^{\#\#}$	18,10±4,90

Notes: $^{\Delta}$ – p<0,05, $^{\Delta\Delta}$ – p<0,01, $^{\Delta\Delta\Delta}$ – p<0,001 compared with patients with MI without DM;
* – p<0,05, ** – p<0,01, ***– p<0,001 n comparison with patients with DM without a history of MI;
$^{\#}$ – p<0,05, $^{\#\#}$ – p<0,01, $^{\#\#\#}$– p<0,001 compared with patients with DM without MI.

(p <0.001), TG (p <0.001), LDLC (p <0.05), LDLC (p<0.05), CA 0.001), Apo B (p <0.05) and the ratio of Apo B/Apo A-1 (p <0.001), compared with non-diabetic postinfarction patients. There was a significantly lower concentration of HDLC (p <0.01), Apo A-1 (p <0.05) and LP (a) – p <0.05 in patients with a history of diabetes mellitus).

When comparing the studied indicators of patients of the main group with patients with isolated type 2 diabetes, significantly higher values of LDLC (p <0.05) and CA (p <0.001), as well as significantly lower concentrations of HDLC (p <0.01) and apo A-1 (p <0.05) in patients of the main group.

In the analysis of lipid metabolism of the comparison groups, the difference in the level of TG (p <0.001), LDLC (p <0.001) and Apo B (p <0.05), which have higher levels in patients with isolated type 2 diabetes, is noteworthy. , and the level of LP (a) - p <0,01, which is significantly higher in postinfarction patients, in contrast to diabetics.

Thus, the results indicate deeper disorders of lipid metabolism in postinfarction patients with diabetes than in non-diabetic postinfarction patients, which may be explained by insulin resistance, hyperinsulinemia and hyperglycemia, which are the pathogenetic basis of type 2 DM. It is known that insulin resistance [13] in the fat cell activates lipolysis, which leads to the release of large amounts of free fatty acids (FA) into the bloodstream. Further, there is an increase in the synthesis of TG and LDL due to the availability of their main substrate, as well as a decrease in the degradation of Apo B. Excessive production of LDL with increased secretion of TG and Apo B leads to the formation of small dense particles of LDL. This subtype of LDL plays an important role in atherogenesis, being more prone to oxidation under conditions of impaired antioxidant defense mechanisms in diabetics [10]. Both LDL and LDL residues and particles carry the Apo B molecule, so such dyslipidemia is characterized by an increase in serum Apo B concentration. Apo B levels are more closely associated with diabetes and insulin resistance than LDL and HDL because they are found in the most atherogenic particles of lipoproteins, and therefore can better predict cardiovascular events in such patients and are recognized as a valuable marker of CVD [20]. Regarding the antiatherogenic class of HDL, recent studies have shown that patients with diabetes not only have a quantitative decrease in these lipoproteins, but also may lose their protective function due to disruption of the structure of protein constituents on the background of prooxidant and proinflammatory phenotype [18]. Thus, HDL in diabetics is less effective in preventing LDL oxidation. Determining the level of Apo A-1 as the main protein of HDL, according to epidemiological and interventional studies, in addition to determining Apo B, allows you to more accurately predict cardiovascular risks than the assessment of conventional lipid parameters [20]. In addition to insulin resistance, hyperglycemia also has a direct negative effect on lipid metabolism in these patients. It was found that the level of modified LDL increases significantly as a result of their glycosylation, which significantly enhances the atherogenic potential of lipoproteins [17].

Therefore, not only quantitative but also qualitative changes of lipids and lipoproteins are used, which increase their proatherogenic effects with corresponding clinical consequences. Thus, routine determination of general lipid profile parameters cannot provide complete information on atherogenic potential in a particular disease.

Today, hypertriglyceridemia in patients with diabetes is considered as a multifactorial process, with each injection of LCD from the periphery into the liver due to insulin resistance is only one component of this process. The decrease in HDL levels in these patients, which is often due to an increase in TG levels and the transition of TG to HDL (in exchange for cholesterol), is likely to be more complex, as the decrease in HDL at normal TG concentrations often changes [9].

Thus, not all pathogenetic mechanisms of diabetic dyslipidemia have been elucidated to date, and this is the subject of further study.

The results also show more pronounced atherogenic changes in the lipid spectrum of the blood in patients with type 2 DM who had a history of MI, compared with patients without MI. The results of the well-known British study UKPDS [19] showed that an increase in LDL cholesterol by 1 mmol/l is associated with an increase in the frequency of CVD endpoints by 57%, and an increase in HDL cholesterol by 0.1 mmol/l – with a decrease in CVD endpoints at 15%. Thus, our data confirm the fact that the increase in the degree of atherogenicity of lipid changes causes cardiovascular events. Therefore, it is important to timely and adequately influence the altered lipid profile in patients with type 2 DM to prevent complications of coronary heart disease and improve cardiovascular prognosis.

The difference in the comparison groups, namely between patients with isolated type 2 diabetes and postinfarction cardiosclerosis without diabetes, in terms of TG, LDL cholesterol and Apo B is explained by the pathogenetic mechanisms of dyslipidemia in diabetes, which were discussed above. As for LP (a), it is considered to be one of the most studied, but still a mysterious lipoprotein. Despite decades of research, the normal physiological role of LP (a) is still unclear. As for pathophysiology, there is more clarity. LP (a) can cause cardiovascular pathology due to proatherogenic LDL cholesterol and stimulate thrombosis due to the thrombogenic properties of Apo A, which are part of it. Thus, numerous studies suggest that high levels of LP (a) are an independent risk factor for atherogenesis and thrombogenesis. The amount of LP (a) is more than 90% determined genetically and depends mainly on the rate

of Apo A biosynthesis and, unlike most lipid risk factors, does not depend on age, sex, diet, living conditions and is very poorly corrected by medication [4, 11, 16].

Thus, going back to our data, we can assume that most patients who suffered from MI and did not have diabetes had a genetically determined high risk of acute coronary complications.

CONCLUSIONS

1. Dyslipoproteinemia in postinfarction patients with type 2 DM is characterized by a decrease in the content of antiatherogenic HDL cholesterol and its protein Apo A-1, moderate hypertriglyceridemia, increased levels of LDL cholesterol, VLDL cholesterol and Apo B, which causes higher values of cholesterol and increases CKD.
2. Elevations in lipid profile parameters such as TG, LDL cholesterol, and Apo B are more associated with the effects of diabetes, while higher concentrations of LP (a) are characteristic of postinfarction non-diabetic patients.

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ОСОБЛИВОСТІ ДИСЛІПОПРОТЕЇНЕМІЇ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ, ЯКІ ПЕРЕНЕСЛИ ІНФАРКТ МІОКАРДУ

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Актуальність. При цукровому діабеті (ЦД) атеросклеротичні бляшки містять більше жиру, в більшому ступені запальнозмінені і демонструють вищий ризик тромбоутворення, ніж в осіб без ЦД. Одним з вагомих факторів розвитку та прогресування атеросклерозу у цих хворих є атерогенна дисліпідемія, яка включає широкий спектр порушень і часто передує виникненню ЦД на декілька років. Тому є актуальним дослідження особливості дисліпідемії у хворих на ЦД, які перенесли інфаркт міокарда (ІМ).

Мета: вивчити зміни показників ліпідного спектру крові, включаючи аполіпопротеїни (Апо А-1, Апо В) та ліпопротеїн (а), у постінфарктних хворих з ЦД 2 типу

Матеріали та методи. Обстежено 119 хворих (77 чоловіків та 42 жінки; середній вік 61,09±0,92 р.), з яких 42 – пацієнти з ішемічною хворобою серця (ІХС), які перенесли ІМ та хворіють на ЦД 2 типу (основна група), 39 хворих з ІМ в анамнезі без супутнього ЦД (І група порівняння) та 38 пацієнтів з ЦД 2 типу без перенесеного ІМ (ІІ група порівняння). Контрольну групу склали 30 практично здорових осіб, зіставних за віком та статтю. Визначали загальний холестерин (ЗХС), тригліцериди (ТГ) та холестерин ліпопротеїдів високої щільності (ХС ЛПВЩ) в сироватці венозної крові ферментативним колориметричним методом. За формулами обчислювали рівень холестерину в ліпопротеїнах дуже низької щільності (ХС ЛПДНЩ); холестерин в ліпопротеїнах низької щільності (ХС ЛПНЩ), коефіцієнт атерогенності (КА). Рівень ліпопротеїну (а) – ЛП (а), Апо А-1 та Апо В визначали методом імунотурбідіметрії. Забір крові у пацієнтів здійснювався натщесерце.

Результати. В основній групі виявлено достовірно вищі показники ЗХС, ТГ, ХС ЛПНЩ, ХС ЛПДНЩ, КА, Апо В та співвідношення Апо В/Апо А-1, порівняно з недіабетичними постінфарктними пацієнтами. При цьому відмічалась достовірно нижча концентрація ХС ЛПВЩ, Апо А-1 та ЛП (а) – у хворих на ЦД з ІМ в анамнезі. При співставленні показників пацієнтів основної групи з хворими на ізольований ЦД 2 типу спостерігались достовірно вищі показники ХС ЛПНЩ та КА, а також достовірно нижчі концентрації ХС ЛПВЩ і апо А-1 у хворих основної групи. При аналізі показників ліпідного обміну груп порівняння виявлена відмінність за рівнем ТГ, ХС ЛПДНЩ і Апо В, що мають вищі рівні у пацієнтів з ізольованим ЦД 2 типу, та рівнем ЛП (а) – що достовірно вищ ий у постінфарктних хворих, на відміну від діабетичних. Отримані результати свідчать про більш глибокі порушення ліпідного обміну у постінфарктних хворих за умови наявності ЦД, ніж у недіабетичних постінфарктних пацієнтів, що може пояснюватись інсулінорезистентністю, гіперінсулінемією та гіперглікемією.

Висновки. Дисліпопротеїнемія у постінфарктних хворих з ЦД 2 типу характеризується зниженням вмісту антиатерогенного ХС ЛПВЩ та його білка Апо А-1, помірною гіпертригліцеридемією, збільшенням рівня ХС ЛПНЩ, ХС ЛПДНЩ та Апо В, що зумовлює вищі значення ЗХС та збільшує КА. Підвищення таких показників ліпідограми, як ТГ, ХС ЛПДНЩ та Апо В, в більшому ступені, пов'язані з впливом ЦД, в той час як вищі концентрації ЛП (а) характерні для постінфарктних недіабетичних хворих.

Ключові слова: цукровий діабет 2 типу, постінфарктний кардіосклероз, дисліпопротеїнемія.

ОСОБЕННОСТИ ДИСЛИПОПРОТЕИНЕМИЯ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА, ПЕРЕНЕСШИХ ИНФАРКТ МИОКАРДА

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Актуальность. При сахарном диабете (СД) атеросклеротические бляшки содержат больше жира, в большей степени воспалительно изменены и демонстрируют более высокий риск тромбообразования, чем у лиц без СД. Одним из весомых факторов развития и прогрессирования атеросклероза у этих больных является атерогенная дислипидемия, которая включает широкий спектр нарушений и часто на несколько лет предшествует возникновению СД. Поэтому актуально исследование особенности дислипидемии у больных СД, перенесших инфаркт миокарда (ИМ).

Цель: изучить изменения показателей липидного спектра крови, включая аполипопротеины (Апо А-1, Апо В) и липопротеин (а), у постинфарктных больных с СД 2 типа

Материалы и методы. Обследовано 119 больных (77 мужчин и 42 женщины, средний возраст 61,09±0,92 г.), из которых 42 – пациенты с ишемической болезнью сердца (ИБС), перенесших ИМ и страдающих СД 2 типа (основная группа), 39 больных с ИМ в анамнезе без сопутствующего СД (I группа сравнения) и 38 пациентов с СД 2 типа без перенесенного ИМ (II группа сравнения). Контрольную группу составили 30 практически здоровых лиц, сопоставимых по возрасту и полу. Определяли общий холестерин (ОХС), триглицериды (ТГ) и холестерин липопротеидов высокой плотности (ХС ЛПВП) в сыворотке венозной крови ферментативным колориметрическим методом. По формулам вычисляли уровень холестерина в липопротеинах очень низкой плотности (ХС ЛПОНП), холестерин в липопротеинах низкой плотности (ХС ЛПНП), коэффициент атерогенности (КА). Уровень липопротеина (а) – ЛП (а), Апо А-1 и Апо В определяли методом имунотурбидиметрии. Забор крови у пациентов осуществлялся натощак.

Результаты. В основной группе выявлены достоверно более высокие показатели ОХС, ТГ, ХС ЛПНП, ХС ЛПОНП, КА, Апо В и соотношение Апо В / Апо А-1 по сравнению с недиабетическими постинфарктными пациентами. При этом отмечалась достоверно более низкая концентрация ХС ЛПВП, Апо А-1 и ЛП (а) – у больных СД с ИМ в анамнезе. При сопоставлении показателей пациентов основной группы и больных только с СД 2 типа наблюдались достоверно более высокие показатели ХС ЛПНП и КА, а также достоверно более низкие концентрации ХС ЛПВП и Апо А-1 у больных основной группы. При анализе показателей липидного обмена групп сравнения выявлены отличия по уровню ТГ, ХС ЛПОНП и Апо В – более высокие уровни их у пациентов с изолированным СД 2 типа; и уровнем ЛП (а) – достоверно выше у постинфарктных больных, в отличие от диабетических. Полученные результаты свидетельствуют о более глубоких нарушениях липидного обмена у постинфарктных больных при наличии СД, чем у недиабетических постинфарктных пациентов, что может объясняться инсулинорезистентностью, гиперинсулинемией и гипергликемией.

Выводы. Дислипопротеинемия у постинфарктных больных с СД 2 типа характеризуется снижением содержания антиатерогенного ХС ЛПВП и его белка Апо А-1, умеренной гипертриглицеридемией, повышением уровня ХС ЛПНП, ХС ЛПОНП и Апо В, что приводит к более высоким значениям ОХС и увеличивает КА. Повышение таких показателей липидограммы, как ТГ, ХС ЛПОНП и Апо В, в большей степени, связаны с влиянием СД, в то время как высокие концентрации ЛП (а) характерны для постинфарктных недиабетических больных.

Ключевые слова: сахарный диабет 2 типа, постинфарктный кардиосклероз, дислипопротеинемия.

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MODERN RESOURCES OF CELIAC DISEASE TREATMENT EFFECTIVENESS IMPROVEMENT

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Relevance. Although monotherapy with a gluten-free diet (BGD) for celiac disease is highly effective, it does not in all cases achieve complete remission of the disease. Therefore, an additional comprehensive examination of patients for the purpose of prescribing reasonable therapy is relevant.

Objective: to study the causes of persistence of clinical symptoms in patients with celiac disease who are on a gluten-free diet for 6 months.

Materials and methods. Patients with celiac disease (n = 41) who were on a gluten-free diet (GFD) for 6 months were studied. The average age is 35.42 ± 0.45 years. Group 1 (n = 17) – patients who subjectively noted a positive dynamics of treatment and with a significant improvement in general condition, but without complete clinical remission. Group 2 (n = 24) – patients with unsatisfactory treatment results, no clinical effect from treatment or weak positive dynamics on the background of GFD. The study included two stages: 1) assessment of patients' compliance and their diet (through the analysis of food diaries) in order to identify disorders of gluten-free diet as the main cause of persistence of clinical symptoms; 2) identification of other causes of persistence of symptoms: exocrine pancreas insufficiency (EPI), lactase deficiency (LD) and the syndrome of increase bacterial growth (SIBR). A C13 triglyceride breath test (IRIS analyzer) was performed to diagnose EPI. To diagnose LD and SIBR in the small intestine, hydrogen breath tests (Micro H2-meter analyzer) were used – a test with lactose and D-xylose, respectively. Also, the titer of antibodies to tissue transglutaminase (TTG) to deaminated gliadin peptides (DPG) was determined in all patients, and their DPG/TTG ratio was calculated.

Results. The main reason for the ineffectiveness of treatment is a violation of gluten-free diet, found in 63.4% of subjects (incompletely formed mushy stool, polyfaeces, steatorrhea; recurrent abdominal pain, bloating, flatulence). Revision of food intake and elimination of sources of latent gluten from the diet of patients with celiac disease allowed to achieve complete serological remission (normalization of titers specific for celiac disease antibodies) in all patients, but complete clinical remission was achieved in only 34.6%. Therefore, it is concluded that there are other causes of incomplete remission of celiac disease associated with concomitant diseases of the digestive tract. Using carbon and hydrogen breath tests, it was found that, in addition to diet, the reasons for the lack of complete remission in patients with celiac disease are EPI (19%), SIBR in the small intestine (16%), LD (47%) and a combination of EPI with SIBR.

Conclusion. The inclusion of respiratory tests (C13-triglyceride, hydrogen with lactose and D-xylose) in a comprehensive examination of patients with celiac disease can significantly improve treatment outcomes and reduce the duration of clinical remission.

Key words: celiac disease, gluten-free diet, breath tests, C13-triglyceride, hydrogen with lactose and D-xylose

Relevance. Celiac disease (gluten enteropathy) is the most studied disease of the small intestine to date, the prevalence of which, according to the World Organization of Gastroenterology (OMGE), averages 1% of the general population. As you know, the only treatment for celiac disease is a gluten-free (agliadin) diet (GFD), based on the complete exclusion from the patient's diet of all foods containing the main protein of cereals (wheat, rye, barley and oats) gluten. The purpose of prescribing GFD is to stop the pathological autoimmune process in the body of a patient with celiac disease in response to the exclusion of gluten from the diet, leading to a gradual restoration of the structure of the affected mucous membrane of the small intestine, and then - the disappearance of clinical manifestations of the disease, normalization of the patient's general condition and prevention of possible complications [1]. With strict and lifelong adherence to the GFD, successfully treated patients become practically healthy.

The high efficiency of a gluten-free diet allows it to be used in monotherapy, as a method of «standard» treatment of a celiac patient and, as a rule, does not require additional inclusion of drugs in the complex therapy. Therefore, traditional attempts at starting (in combination with a gluten-free diet) prescribing drugs without appropriate medical indications (no concomitant diseases) are often unjustified. However, the existing experience in the management of patients with celiac disease indicates that not in all cases doctors are able to achieve complete remission of the disease, which prompts additional examination and, if the reasons are identified, justified therapy.

These methods, which allow to optimize the treatment of patients with gluten enteropathy, today are breath tests,

which are widely used in the clinic of internal medicine, especially in gastroenterology. Carbon breath tests have long been known and are used to diagnose Helicobacter pylori infection (test with urea), pancreatic diseases (triglyceride, amylase), liver detoxification function (metacetin), to determine the motor-evacuation function of the stomach (octanoic), etc. [2, 3, 4, 5]. The use of hydrogen breath tests became available somewhat later, but they also took their place in the diagnosis of diseases of the digestive system and are widely used to diagnose enteropathies, disaccharidase deficiency, syndrome of bacterial overgrowth in the small intestine, etc. [6].

Several attempts have been made to use hydrogen breath tests in the diagnosis of celiac disease [7, 8]. This concerned various tests - with lactulose, D-xylose, sorbitol, etc. an early peak in hydrogen concentration has been reported on a lactulose breath test in patients with celiac disease [9]. Described the use of a hydrogen test with D-xylose for the diagnosis of celiac disease in different age groups [10]. It has been established that this test can be used to improve screening for celiac disease (namely, to identify the consequences of atrophy of the mucous membrane of the small intestine and malabsorption) [11]. Used lactose hydrogen breath test to assess the effectiveness of celiac disease treatment [12]. The place of the hydrogen test with sorbitol has been reported both in the diagnosis of celiac disease (since the latter reflects the severity of atrophic damage to the mucous membrane of the small intestine) and in assessing the effectiveness of a gluten-free diet. According to research results, the sorbitol test reflects the stage of restoration of the structure of the mucous membrane against the background of a diet, which means that it can be recommended as a simple, affordable method for assessing the effectiveness of treatment [13, 14].

Objective: To study the causes of persistence of clinical symptoms in celiac patients on a gluten-free diet for 6 months.

MATERIALS AND METHODS

The study included celiac patients (n = 41) who had been on a gluten-free diet for 6 months. The average age of those included in the study was 35.42 + 0.45 years. Women prevailed over men, accounting for a quantitative ratio of 1.6 : 1.

All patients showed positive dynamics of treatment: clinically – an improvement in the general condition, a decrease in the frequency of defecation, a tendency to normalize stool (a decrease in the frequency of bowel movements up to 3.5 times a day) in the absence of a fully formed stool (mostly mushy, a tendency to polyfecalia, steatorrhea), stabilization of body weight, increased BMI, 30% had recurrent abdominal pain, bloating, flatulence); laboratory – normalization/reduction of antibody titers at least three times (antibodies to tissue transglutaminase (TTG), to deaminated peptides of gliadin (DPG) were determined, the DPG/TTG ratio was calculated). Thus, the persisting symptoms and the absence of complete laboratory remission (normalization of serological biomarker titers for celiac disease) did not allow the treatment results to be regarded as satisfactory and required identification of possible causes.

The included patients were divided into two groups. Group 1 (n = 17) was represented by patients who subjectively noted positive dynamics of treatment and with a significant improvement in their general condition, but without complete clinical remission. Group 2 (n = 24) - patients with unsatisfactory results of treatment, no clinical effect of treatment, or weak positive dynamics against the background of GFD.

The research program included two main stages:

1 – assessment of compliance of patients and their diet (through analysis of food diaries) in order to identify violations of a gluten-free diet as the main cause of persistence of clinical symptoms,

2 – identification of other causes of persistence of symptoms, namely, exocrine pancreatic insufficiency (EPI), lactase deficiency (LD) and syndrome of increase bacterial growth (SIBR) using modern carbon and hydrogen breath tests.

In order to diagnose EPI, a C13 triglyceride breath test was performed. The technique of the test is that before the test, the intake of enzyme preparations is stopped for at least 72 hours before the test. The procedure is performed in the morning on an empty stomach. The subject makes the first exhalation into a sealed, plastic bag. After that, a so-called «test» breakfast is eaten, consisting of 100 g of white bread, butter in terms of 0.25 g/kg of body weight, to which C13-labeled triglycerides were previously added at the rate of 4 mg/kg of patient weight. Subsequent samples of exhaled air are collected in bags every 30 minutes for 6 hours, and then analyzed on an infrared spectrometer by IRIS by Wagner Analysen Technik (Germany).

Indicators of the maximum concentration of CO2, recorded between 150 and 210 minutes of the test, above 8%, as well as the cumulative dose of released 13CO2 above 23% for the entire period of the test, indicate normal exocrine function of the pancreas. The maximum concentration of 13CO2, recorded after 210 minutes (in our study – by 271 ± 16 minutes), at a normal cumulative dose of 13CO2, indicates a latent EPI. The reduced maximum concentration of 13CO2, which was 4.7 ± 1.4% and recorded between 150 and 210 minutes of the test, with a reduced cumulative dose of 13CO2 released (18.1 ± 5.9%), indicates a moderate EPI. A decrease in the maximum concentration to 4.8 ± 1.3%, recorded at 275 ± 27 minutes, with a cumulative dose of 16.7 ± 3.5%, indicates a pronounced EPI.

To diagnose lactase deficiency and SIBR in the small intestine, we used hydrogen breath tests (Micro H2-meter analyzer) – a test with lactose and D-xylose, respectively. The principle of carrying out hydrogen tests is that the hydrogen formed in the intestine by its microflora is

included in the intestinal gases. On an empty stomach, hydrogen is formed in the large intestine in a small amount (0.24 ml/min.), After a meal, its production increases 7-20 times [15, 16, 17]. Approximately 15% of the generated hydrogen is excreted by the lungs after being absorbed into the blood. Based on the concentration of hydrogen in the exhaled air, conclusions are drawn about its amount in the intestine [18, 19, 20]. To conduct hydrogen breath tests, we used the techniques [19, 20], based on the determination of the concentration of hydrogen in the air exhaled by the subject before and after a special food load. The methods for conducting hydrogen tests are of the same type. The average test duration is 2-3 hours.

Diagnosis of lactase deficiency (test with lactose) is based on the fact that lactose, entering the intestine, under the influence of bacteria, promotes the additional release of hydrogen, which, after absorption, also enters the bloodstream, and then reaches the lungs with gases and is exhaled. An increase in the concentration of lactose in the exhaled air above 20 ppm from the initial one indicates the presence of lactose malabsorption [20]. The D-xylose breath test was used to diagnose SIBR. Interpretation of the results: the D-xylose test was considered positive when the hydrogen concentration in the patient's exhaled air increased by 20 ppm from baseline in 40-60 minutes and indicated the presence of SIBR in the small intestine.

The results were statistically processed.

RESULTS AND ITS DISCUSSION

In group 1 (patients with incomplete clinical remission), the results of serological analysis made it possible to divide patients into subgroups (Fig. 1):

1A (n = 8) – patients with elevated antibody titers, or seropositive patients (SPP);

1B (n = 9) – patients with complete normalization of serological parameters, or seronegative patients (SNP).

In subgroup 1A, the analysis of the reasons for the persistence of clinical symptoms was carried out, which indicated periodic disturbances in the diet and (or) contamination of foods with gluten (based on the analysis of food diaries), which was reflected in the absence of normalization of antibody titers against the background of the received treatment. The analysis of the diet of patients of subgroup 1B testified to strict adherence to the diet, which was confirmed by the indicators of the immunological response and the complete normalization of antibody titers. Patients in subgroup 1B had a high compliance, strictly followed the recommendations, however, it was not possible to achieve complete remission during the follow-up period.

In group 2 (patients with unsatisfactory treatment results), no significant clinical dynamics was observed during the observation period, both according to the results of an objective examination of patients and according to their subjective assessments. Group 2, depending on the dynamics of the immunological response to treatment, was also divided into two subgroups (Fig. 1):

2A (n = 18) – seropositive patients;

2B (n = 6) – seronegative patients.

As can be seen from Figure 1, the same pattern of distribution into subgroups was revealed in both groups. Namely: the dependence of treatment results on compliance, fulfillment of the requirements of the agliadin diet and, as a result, normalization of antibody titers. 26 (63.4%) patients from the general group included in the study were dieting, which was determined by the leading cause of persistence of clinical symptoms. The results obtained correspond to modern ideas about the possibility of achieving a positive immunological response and restoration of antibody titers only in response to the complete elimination of gluten from the diet [1], and the gluten-free diet itself is the main decisive factor in achieving complete clinical and laboratory recovery. 15 (36.6%) examined (subgroups 1B and 2B) did not break the diet, which was confirmed by serological remission.

Therefore, the first step in correcting the persistence of clinical symptoms in patients with celiac disease of subgroups 1A and 2A (n = 26) was the actual correction of the diet based on the revision of food diaries and the search for possible sources of food contamination with gluten. As a result of the revised dietary recommendations, in 9 (34.6%) patients, antibody titers completely normalized over 3 months of treatment, complaints disappeared, which indicated that a complete clinical and laboratory remission was achieved. In 17 (65.4%) patients, as a result of diet correction, antibody titers also returned to normal, however, complete clinical remission was still not achieved (clinical symptoms persisted) (Fig. 2).

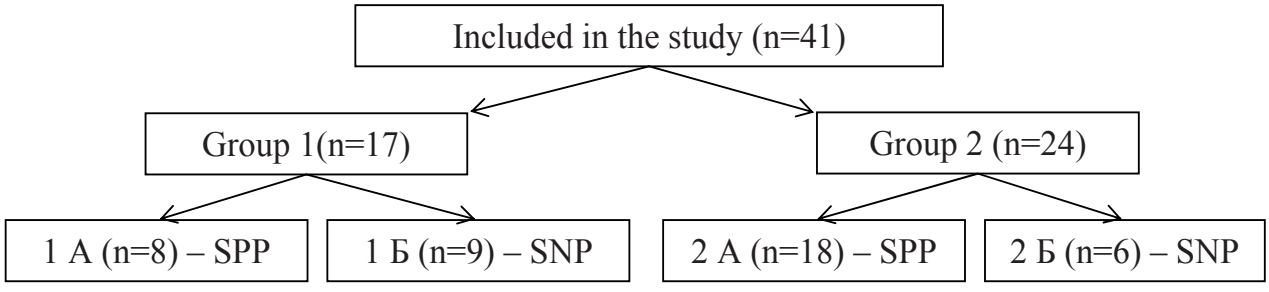

Fig. 1. Distribution of celiac disease patients with persistent clinical symptoms depending on the serological response to treatment (SPP - seropositive patients; SNP - seronegative patients)

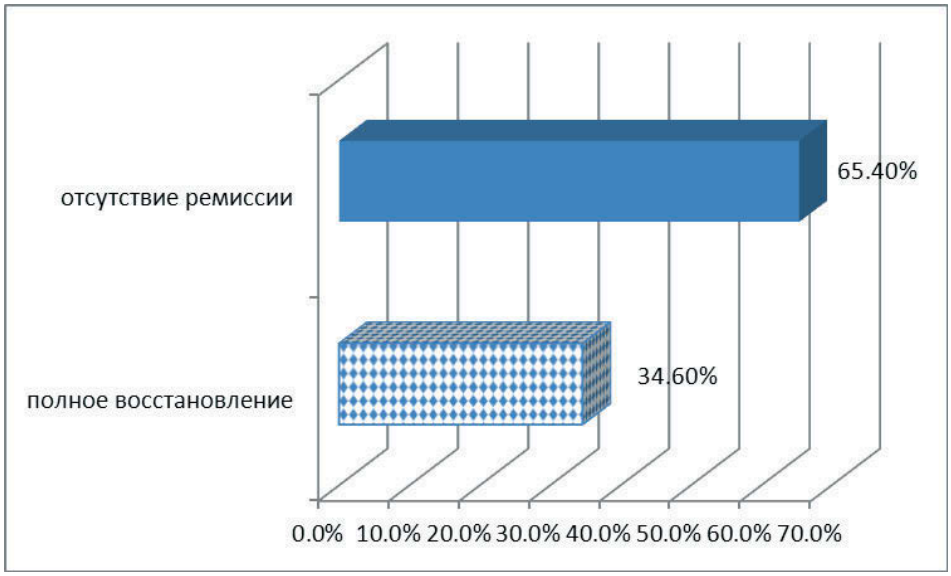

Fig. 2. Results of diet correction in celiac patients with persistent clinical symptoms (n=26)

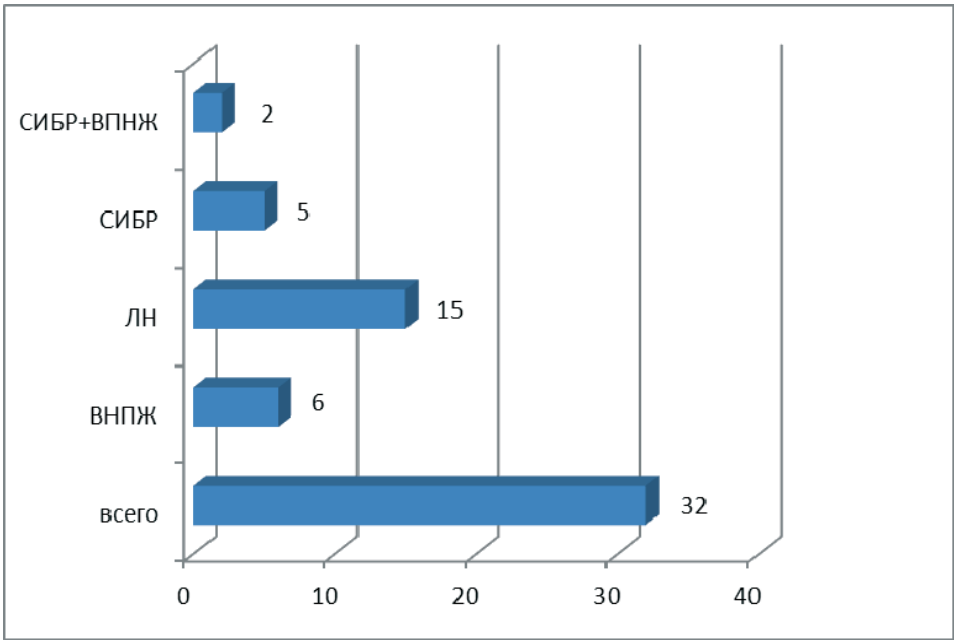

Fig. 3. The structure of the identified causes of persistence of clinical symptoms in seronegative celiac patients (n=32)

Thus, a violation of the diet is the first, but not the only reason for the persistence of clinical symptoms in celiac patients and requires a search for other causes. To resolve this issue, we conditionally combined patients of the first and second stages of the study, forming a group (n = 32) of seronegative patients, which included 15 seronegative patients (subgroups 1B and 2B) who did not break the diet and were identified in the first stage of the study, and 17 SNPs with persistence of symptoms, which persisted despite the correction of the gluten-free diet and restoration of antibody titers.

We made the assumption that the possible reasons for the persistence of clinical symptoms in SNP with persistence of symptoms could be exocrine pancreatic insufficiency, lactase deficiency and syndrome of bacterial overgrowth in the small intestine. Diagnosis of the above pathology was carried out using C13-triglyceride carbon and hydrogen breath tests with lactose and D-xylose, according to the methods described above.

As a result of the study, it was revealed that 6 patients (19%) had exocrine pancreatic insufficiency, verified by the results of the C13-triglyceride breath test. As a result of the hydrogen test with lactose, lactase deficiency was detected in 15 (47%) of the examined. SIBR was established in 5 (16%) patients. In two patients of this group, a combination of severe exocrine pancreatic

insufficiency with a syndrome of bacterial overgrowth in the small intestine was revealed, which was the objective reason for the lack of effect of the agliadin diet in monotherapy (Fig. 3)

Correction of concomitant diseases of the gastrointestinal tract revealed during the study (prescribing enzyme preparations in adequate doses, lactose-free diet in combination with prescribing lactase preparations and sanitation of the small intestine with the prescription of rifaximin in standard doses), made it possible to achieve complete clinical remission within one month of treatment.

So, as a result of our study, we investigated the causes of persistence of clinical symptoms in 41 celiac patients who had been on a gluten-free diet for 6 months. The main reason for the lack of effectiveness of treatment is the violation of a gluten-free diet, identified in 63.4% of the examined. Revision of food intake and elimination of hidden gluten sources from the diet of celiac disease patients made it possible to achieve complete serological remission (normalization of the titers of celiac disease-specific antibodies) in all patients, however, complete clinical remission was achieved only in 34.6%. As a result, we drew conclusions about the existence of other causes of incomplete remission of celiac disease, most likely associated with concomitant diseases of the digestive tract.

Using modern carbon and hydrogen breath tests (C13-triglyceride for the diagnosis of EPI, lactose for detecting lactase deficiency, and the D-xylose test used for diagnosing SIBR), a further analysis of the causes of persistence of clinical symptoms in patients strictly adhering to the requirements of a gluten-free diet was carried out. As a result, it was found that, in addition to the violation of the diet, the reasons for the lack of complete remission in patients with celiac disease are exocrine pancreatic insufficiency (19%), bacterial overgrowth syndrome in the small intestine (16%), lactase deficiency (47%) and the combination of EPI with SIBR.

CONCLUSIONS

The inclusion of breath tests (C13-triglyceride, hydrogen with lactose and D-xylose) in a comprehensive examination of celiac disease patients can significantly improve the results of treatment and shorten the onset of clinical remission.

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СУЧАСНІ МОЖЛИВОСТІ ПОЛІПШЕННЯ ЕФЕКТИВНОСТІ ЛІКУВАННЯ ЦЕЛІАКІЇ

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Актуальність. Хоча монотерапія безглютеновою дієтою (БГД) при целіакії і є високоефективною, але все ж таки не у всіх випадках дозволяє досягти повної ремісії захворювання. Тому актуальним є додаткове комплексне обстеження хворих з метою призначення обгрунтованої терапії.

Мета: вивчити причини персистенції клінічної симптоматики у хворих на целіакію, що знаходяться на безглютеновій дієті 6 місяців.

Матеріали та методи. Досліджені хворі на целіакію (n=41), що знаходилися на безглютеновій дієті 6 місяців. Середній вік – 35,42±0,45 років. Група 1 (n=17) – пацієнти, які суб'єктивно відзначали позитивну динаміку лікування і достовірне поліпшення загального стану, але без повної клінічної ремісії. Група 2 (n=24) – пацієнти з незадовільними результатами лікування, відсутністю клінічного ефекту від лікування або слабкою позитивною динамікою на тлі БГД. Дослідження включало два етапи: 1) оцінка комплайєнса пацієнтів та їх раціону харчування (за допомогою аналізу харчових щоденників) з метою виявлення порушення безглютенової дієти, як основної причини персистенції клінічної симптоматики; 2) виявлення інших причин персистенції симптоматики: зовнішньосекреторної недостатності підшлункової залози (ЗНПЖ), лактазної недостатності (ЛН) і синдрому надлишкового бактеріального росту (СНБР). З метою діагностики ЗНПЖ виконувався С13-тригліцеридний дихальний тест (аналізатор IRIS). Для діагностики ЛН і СНБР в тонкій кишці застосовували водневі дихальні тести (аналізатор Micro H2-meter) – тест з лактозою і D-ксилозою, відповідно. Також у всіх пацієнтів визначали титр антитіл до тканинної трансглутамінази (ТТГ), до дезамінованих пептидів гліадину (ДПГ), розраховували їх співвідношення ДПГ / ТТГ.

Результати. Основною причиною недостатньої ефективності лікування є порушення безглютенової дієти, виявлене у 63,4% обстежених (не в повному обсязі сформований кашкоподібний стілець, поліфекалія, стеаторея; рецидивуюча біль в животі, здуття, флатуленція). Перегляд споживаних продуктів харчування і виключення з раціону хворих на целіакію джерел прихованого глютену дозволив досягти повної серологічної ремісії (нормалізації титрів специфічних для целіакії антитіл) у всіх пацієнтів, однак повна клінічна ремісія була досягнута тільки у тільки 34,6%. Тому зроблені висновки про існування інших причин неповної ремісії целіакії, пов'язаних із супутніми захворюваннями органів травного каналу. За допомогою вуглецевого і водневих дихальних тестів встановлено, що, крім порушення дієти, причинами відсутності повної ремісії у хворих на целіакію є ЗНПЖ (19%), СНБР в тонкій кишці (16%), ЛН (47%) і комбінація ЗНПЖ з СНБР.

Висновок. Включення в комплексне обстеження хворих на целіакію дихальних тестів (С13-тригліцеридного, водневого з лактозою і D-ксилозою) може значно поліпшити результати лікування і скоротити терміни настання клінічної ремісії.

Ключові слова: целіакія, безглютенова дієта, дихальні тести, С13-тригліцеридний, водневий з лактозою і D-ксилозою

СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ ПОВЫШЕНИЯ ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ ЦЕЛИАКИИ

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Актуальность. Хотя монотерапия безглютеновой диетой (БГД) при целиакии и является высокоэффективной, но всё же не во всех случаях позволяет достичь полной ремиссии заболевания. Поэтому актуальным является дополнительное комплексное обследование больных с целью назначения обоснованной терапии.

Цель: изучить причины персистенции клинической симптоматики у больных целиакией, находящихся на безглютеновой диете 6 месяцев.

Материалы и методы. Исследованы больные целиакией (n=41), находившиеся на безглютеновой диете 6 месяцев. Средний возраст – 35,42±0,45 лет. Группа 1 (n=17) – пациенты, субъективно отмечавшие положительную динамику лечения и с достоверным улучшением общего состояния, но без полной клинической ремиссии. Группа 2 (n=24) – пациенты с неудовлетворительными результатами лечения, отсутствием клинического эффекта от лечения или слабой позитивной динамикой на фоне БГД. Исследование включало два этапа: 1) оценка комплайенса пациентов и их рациона питания (посредством анализа пищевых дневников) с целью выявления нарушения безглютеновой диеты, как основной причины персистенции клинической симптоматики; 2) выявление других причин персистенции симптоматики: внешнесекреторной недостаточности поджелудочной железы (ВНПЖ), лактазной недостаточности (ЛН) и синдрома избыточного бактериального роста (СИБР). С целью диагностики ВНПЖ выполнялся С13-триглицеридный дыхательный тест (анализатор IRIS). Для диагностики ЛН и СИРБ в тонкой кишке применяли водородные дыхательные тесты (анализатор Micro H2-meter) – тест с лактозой и D-ксилозой, соответственно. Также у всех пациентов определяли титр антител к тканевой трансглутаминазе (ТТГ), к дезаминированным пептидам глиадина (ДПГ), рассчитывали их соотношение ДПГ/ТТГ.

Результаты. Основной причиной недостаточной эффективности лечения является нарушение безглютеновой диеты, выявленное у 63,4% обследованных (не полностью сформированный кашицеобразный стул, полифекалия, стеаторея; рецидивирующая боль в животе, вздутие, флатуленция). Пересмотр потребляемых продуктов питания и исключение из рациона больных целиакией источников скрытого глютена позволил достичь полной серологической ремиссии (нормализации титров специфичных для целиакии антител) у всех пациентов, однако полная клиническая ремиссия была достигнута только у только 34,6%. Поэтому сделаны выводы о существовании других причин неполной ремиссии целиакии, связанных с сопутствующими заболеваниями органов пищеварительного канала. При помощи углеродного и водородных дыхательных тестов установлено, что, помимо нарушения диеты, причинами отсутствия полной ремиссии у больных целиакией являются ВНПЖ (19%), СИБР в тонкой кишке (16%), ЛН (47%) и комбинация ВНПЖ с СИБР.

Вывод. Включение в комплексное обследование больных целиакией дыхательных тестов (С13-триглицеридного, водородного с лактозой и D-ксилозой) может значительно улучшить результаты лечения и сократить сроки наступления клинической ремиссии.

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INDICATORS OF QUALITY OF LIFE OF PATIENTS WITH CHRONIC KIDNEY DISEASE STAGE II-IV

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Relevance. Chronic diseases have a long duration and rather slow progression, and people who have such diseases want not only to live longer, but also to live better. Therefore, quality of life (QOL) is one of the most important health issues for the treatment of chronic diseases.

Objective: to determine the features of QOL in patients with chronic kidney disease (CKD) stage II-IV.

Materials and methods. In 171 patients with CKD of II-IV centuries, in addition to general clinical and laboratory studies, QOL was studied using a questionnaire to assess the quality of life of SF-36. The questionnaire contains 36 questions of the main module, supplemented by multi-point scales aimed specifically at patients with CKD. The answers were evaluated in points - from 0 to 100. The higher the score, the better the patient's QOL. The total components were also calculated: physical total component, mental total component, total points. The obtained research data were subjected to statistical processing, which included parametric (t-test for samples with unrelated variants) and non-parametric (Mann-Whitney method) methods, correlation analysis was used.

Results. Most QOL indicators worsen significantly with the progression of CKD. The indicators of total QOL, as well as the indicator «the impact of the disease on everyday life» are most significantly reduced. Age correlates as much as possible with most indicators of QOL in patients with CKD. With age, the QOL of patients decreases, but the manifestations of the disease increase and the mental and physical condition of patients deteriorates. QOL parameters are probably directly and moderately correlated with hemoglobin levels. Most QOL parameters are significantly moderately correlated with systolic blood pressure and diastolic blood pressure. It is assumed that the correction of anemia and blood pressure control, in addition to a positive effect on disease progression and the occurrence and development of complications, will also improve QOL. There were no significant differences in the assessment of QOL in men and women.

Conclusions. QOL indicators decrease with the progression of CKD. Age, hemoglobin level, blood pressure affect QOL.

Key words: chronic kidney disease, progression, quality of life, SF-36 questionnaire.

Relevance. Increasing life expectancy and advances in medical science have led to problems related to chronic diseases in many countries, including Ukraine. Chronic diseases have a long duration and rather slow progression, and people who have such diseases want not only to live longer, but also to live better. Therefore, quality of life (QOL) is one of the most important health issues for the treatment of chronic diseases.

It is advisable to study the QOL of patients with kidney disease as a typical example of a chronic disease. The daily life of patients with kidney disease is often limited to factors that are common to other chronic diseases, and these factors can easily reduce QOL. In addition, the number of patients with chronic kidney disease (CKD) is growing worldwide [1, 2], in particular in Ukraine [3]. Researchers at the United States Renal Data System Coordinating Center predict that in the coming years, 712 290 patients will have end-stage renal disease each year, 136,166 new cases of CKD and 107 760 cases of death from CKD will be reported [4].

Previous studies of QOL in patients with kidney disease have mainly focused on dialysis patients [5, 6].

Objective: to determine the features of QOL in patients with chronic kidney disease (CKD) stage II-IV.

MATERIALS AND METHODS

The observational study included 171 patients with stage II-IV CKD (59 people with CKD stage II, 57 people with CKD stage III, 55 people with CKD stage IV), aged 24 to 75 years, including 87 men and 84 women. All patients were treated at the Kyiv City Research and Practice Center for Nephrology and Hemodialysis of the Kyiv City Clinical Hospital № 3, which is the clinical base of the Department of Efferent Technologies of the Institute of Nephrology of the National Academy of Medical Sciences of Ukraine.

All subjects, in addition to the generally accepted clinical, laboratory and instrumental research methods, were studied for QOL indicators.

The QOL study was performed using the SF-36 quality of life questionnaire [7]. The questionnaire contains 36 questions of the main module, supplemented by multi-point scales aimed specifically at patients with CKD.

All examined patients filled out a questionnaire with a consistent factor-by-factor evaluation of the results and the calculation of the individual QOL in points (the higher the score, the better the QOL of the patient). Responses were evaluated in points (from 0 to 100).

The results are obtained on scales:

symptom/problems (symptoms of kidney disease) – «symptoms of kidney disease» (12 points: №№ 17-28);

the impact of kidney disease on everyday life – «effect of kidney disease» (8 points: №№ 29-36);

severity of the disease – burden of kidney disease (4 points: №№ 13-16);

SF-12 (№№ 1-12) is a short form of general health assessment.

Also calculate the following total components:

physical total component – «Physical health composite» (№№ 1-5, 8);

mental total component – «Mental health composite» (№№ 6-7, 9-12);

the total amount of points.

The obtained research data were subjected to statistical processing, which included parametric (t-test for samples with unrelated variants) and nonparametric (Mann-Whitney method) methods, correlation analysis was used. Data were processed on a personal computer using computer applications: Microsoft Excel 2007, Statistica 7.0 and the standard version of SPSS 16.0 (USA). Data are presented as mean (M) ± mean deviation (SD). The difference was considered significant when the significance level $p < 0.05$ was reached.

RESULTS AND DISCUSSION

The study examined the relationship between quality of life and its components with disease progression, as well as the relationship with clinical and laboratory parameters such as age, sex, hemoglobin level, glomerular filtration rate (GFR), systolic blood pressure levels. (SBP) and diastolic blood pressure (DBP).

At the same time, it was found that most QOL indicators significantly deteriorate with the progression of CKD (Table 1). The indicators of total QOL, as well as the indicator «the impact of the disease on everyday life» are most significantly reduced.

It was found that age is most significantly correlated with most indicators of QOL (Table 2).

Table 2

The results of the correlation analysis between SF-36 and the age of patients

Indicators of SF-36	r	p
Total QOL	– 0,32	0,001
Symptoms of kidney disease	– 0,33	0,001
The impact of the disease on everyday life	– 0,1	0,5
The severity of the disease	– 0,08	0,6
SF-12	– 0,38	0,001
Physical total component	– 0,41	0,001
Mental total component	– 0,42	0,001

According to the obtained research results, with age the QOL of patients decreases, but the manifestations of the disease increase and the mental and physical condition of patients deteriorates ($p < 0.05$).

Differences in the quality of life index depending on the sex of patients were studied (Table 3).

It should be noted that no significant differences in the assessment of QOL in men and women in our study were found (p0,05).

Anemia significantly affects the progression of CKD and overall and cardiovascular mortality. We studied the relationship between QOL and hemoglobin levels. The results of the correlation analysis of the relationship between QOL and hemoglobin levels are presented in table 4.

The obtained data show that QOL parameters are probably and directly moderately correlated with hemoglobin levels. That is, in patients with more severe anemia, the QOL values are the lowest.

Table 1

Indicators of SF-36 with the progression of CKD

Indicators of SF-36	Stages of CKD			p
	II	III	IV	
Total QOL	79,4±12,8	74,4±13,6	70,7±11,6	0,001
Symptoms of kidney disease	85,2±12,1	79,5±13,9	74,0±10,9	0,001
The impact of the disease on everyday life	86,9±13,2	83,1±12,9	75,7±14,5	0,001
The severity of the disease	79,7±13,7	72,7±15,1	59,6±12,8	0,001
SF-12	68,1±10,2	62,1±11,5	56,4±10,8	0,001
Physical total component	51,3±10,1	49,8±10,6	41,5±11,5	0,001
Mental total component	40,4±9,8	37,9±10,5	35,1±10,3	0,021

Note: data are presented as M ± SD

Table 3

Dependence of QOL indicators on the sex of patients

Scales SF-36	Points	
	in men	in women
Total QOL	74,6±13,1	74,9±12,6
Symptoms of kidney disease	79,4±12,4	80,6±12,1
The impact of the disease on everyday life	82,8±14,3	84,4±13,1
The severity of the disease	74,8±11,1	76,6±13,9
SF-12	68,6±9,8	64,1±14,2
Physical total component	49,8±12,3	49,6±11,8
Mental total component	37,2±10,2	39,6±10,6

Table 4

Results of the analysis of correlations between SF-36 and hemoglobin levels

Indicators of SF-36	r	p
Total QOL	0,45	0,001
Symptoms of kidney disease	0,31	0,02
The impact of the disease on everyday life	0,34	0,002
The severity of the disease	0,38	0,001
SF-12	0,34	0,007
Physical total component	0,6	0,001
Mental total component	0,51	0,001

Table 5

Results of correlation analysis of the relationship between SF-36 and GFR

Indicators of SF-36	r	p
Total QOL	0,44	0,001
Symptoms of kidney disease	0,38	0,001
The impact of the disease on everyday life	0,16	0,06
The severity of the disease	0,25	0,03
SF-12	0,45	0,001
Physical total component	0,39	0,001
Mental total component	0,41	0,001

Table 6

Results of correlation analysis of the relationship between SF-36 and SBP

Indicators of SF-36	r	p
Total QOL	– 0,34	0,001
Symptoms of kidney disease	– 0,28	0,001
The impact of the disease on everyday life	– 0,16	0,08
The severity of the disease	– 0,23	0,02
SF-12	– 0,4	0,001
Physical total component	–0,36	0,001
Mental total component	– 0,37	0,001

Table 7

Results of correlation analysis of the relationship between SF-36 and DBP

Indicators of SF-36	r	p
Total QOL	– 0,48	0,001
Symptoms of kidney disease	– 0,31	0,001
The impact of the disease on everyday life	– 0,27	0,06
The severity of the disease	– 0,29	0,02
SF-12	– 0,47	0,001
Physical total component	– 0,46	0,001
Mental total component	– 0,41	0,001

The results of the study of the correlations between the level of GFR and QOL indicators are given in table 5.

The obtained data correlate with the results obtained in the study of changes in QOL indicators with the progression of CKD, and show that most of the QOL indicators are likely and directly moderately correlated with GFR. That is, patients with more preserved renal function have the highest QOL.

The results of the study of the correlations between the levels of SBP and DBP, on the one hand, and QOL indicators, on the other, are presented in Tables 6 and 7.

The obtained data show that the majority of QOL indicators are significantly moderately correlated with SBP and DBP.

Thus, the obtained data suggest that the correction of anemia and blood pressure control, in addition to a positive effect on disease progression and the occurrence and development of complications, will also improve QOL.

CONCLUSIONS

Most quality of life indicators deteriorate significantly with the progression of chronic kidney disease. The indicators of the total quality of life, as well as the indicator «the impact of the disease on everyday life» are most significantly reduced.

Age is most significantly correlated with most indicators of quality of life in patients with chronic kidney disease. With age, the quality of life of patients decreases, but the manifestations of the disease increase and the mental and physical condition of patients deteriorates.

Quality of life indicators probably and directly moderately correlate with hemoglobin levels.

Most quality of life indicators are significantly moderately correlated with systolic blood pressure and diastolic blood pressure.

The data suggest that the correction of anemia and blood pressure control, in addition to a positive impact on disease progression and the occurrence and development of complications, will also improve the quality of life.

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ПОКАЗНИКИ ЯКОСТІ ЖИТТЯ У ХВОРИХ НА ХРОНІЧНУ ХВОРОБУ НИРОК II-IV СТАДІЇ

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Актуальність. Хронічні захворювання мають довгу тривалість і досить повільне прогресування, і люди, які мають такі захворювання, бажають жити не тільки довше, але й жити краще. Тому якість життя (ЯЖ) постає одним з найбільш важливих питань у сфері охорони здоров'я для лікування хронічних захворювань.

Мета: визначити особливості показників ЯЖ у хворих на хронічну хворобу нирок (ХХН) II-IV стадії.

Матеріали та методи. У 171 хворого на ХХН II-IV ст., окрім загальноклінічного та лабораторного дослідження, була вивчена ЯЖ за допомогою опитувальника оцінки якості життя SF-36. Опитувальник містить 36 питань основного модуля, доповнених багатопунктовими шкалами, націленими конкретно на хворих з ХХН. Відповіді оцінювали в балах – від 0 до 100. Чим вищий бал, тим ліпше ЯЖ хворого. Також розраховували сумарні компоненти: фізичний сумарний компонент, психічний сумарний компонент, загальну суму балів. Отримані дані досліджень були піддані статистичній обробці, що включала параметричні (t-тест для вибірок з незв'язаними варіантами) і непараметричні (метод Манна-Уітні) методи, застосовувався кореляційний аналіз.

Результати. Більшість показників ЯЖ достовірно погіршуються з прогресуванням ХХН. Найбільш суттєво знижуються показники сумарної ЯЖ, а також показник «вплив захворювання на повсякденне життя». Вік максимально значимо корелює з більшістю показників ЯЖ хворих на ХХН. З віком ЯЖ пацієнтів зменшується, проте збільшуються прояви захворювання та погіршується психічний та фізичний стан пацієнтів. Показники ЯЖ вірогідно та прямо помірно корелюють із рівнем гемоглобіну. Більшість показників ЯЖ достовірно помірно корелюють із систолічним артеріальним тиском та діастолічним артеріальним тиском. Припускається, що корекція анемії та контроль артеріального тиску, окрім позитивного впливу на прогресування захворювання та виникнення та розвиток ускладнень, також дозволять поліпшити ЯЖ. Не виявлено достовірних відмінностей в оцінці ЯЖ у чоловіків та жінок.

Висновки. Показники ЯЖ знижуються з прогресуванням ХХН. Вік, рівень гемоглобіну, артеріального тиску впливають на ЯЖ.

Ключові слова: хронічна хвороба нирок, прогресування, якість життя, опитувальник SF-36.

ПОКАЗАТЕЛИ КАЧЕСТВА ЖИЗНИ У БОЛЬНЫХ ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК II-IV СТАДИИ

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Актуальность. Хронические заболевания имеют большую продолжительность и довольно медленное прогрессирование, и люди, которые имеют такие заболевания, хотят жить не только дольше, но и жить лучше. Поэтому качество жизни (КЖ) выступает одним из наиболее важных вопросов в сфере здравоохранения для лечения хронических заболеваний.

Цель: определить особенности показателей КЖ у больных хронической болезнью почек (ХБП) II-IV стадии.

Материалы и методы. У 171 больного ХБП II-IV ст., кроме общеклинического и лабораторного исследования, было изучено КЖ с помощью опросника оценки качества жизни SF-36. Опросник содержит 36 вопросов основного модуля, дополненных многопунктовыми шкалами, нацеленными именно на больных с ХБП. Ответы оценивали в баллах – от 0 до 100. Чем выше балл, тем лучше КЖ больного. Также рассчитывали суммарные компоненты: физический суммарный компонент, психический суммарный компонент, общую сумму баллов. Полученные данные исследований были подвергнуты статистической обработке, включающей параметрические (t-тест для выборок с несвязанными вариантами) и непараметрические (метод Манна-Уитни) методы, применялся корреляционный анализ.

Результаты. Большинство показателей КЖ достоверно ухудшаются с прогрессированием ХБП. Наиболее существенно снижаются показатели суммарной КЖ, а также показатель «влияние заболевания на повседневную жизнь». Возраст максимально значимо коррелирует с большинством показателей КЖ больных ХБП. С возрастом КЖ пациентов уменьшается, однако увеличиваются проявления заболевания и ухудшается психическое и физическое состояние пациентов. Показатели КЖ достоверно и прямо умеренно коррелируют с уровнем гемоглобина. Большинство показателей КЖ достоверно умеренно коррелируют с систолическим артериальным давлением и диастолическим артериальным давлением. Предполагается, что коррекция анемии и контроль артериального давления, кроме положительного влияния на прогрессирование заболевания и возникновение и развитие осложнений, также позволят улучшить КЖ. Не выявлено достоверных различий в оценке КЖ у мужчин и женщин.

Выводы. Показатели КЖ снижаются с прогрессированием ХБП. Возраст, уровень гемоглобина, артериального давления влияют на КЖ.

Ключевые слова: хроническая болезнь почек, прогрессирование, качество жизни, опросник SF-36

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OPERATIVE TECHNIQUES AND APPROACHES IN COMPLETE ARTERIAL REVASCULARIZATION IN MULTIVESSEL CORONARY ARTERY DISEASE. Review

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Relevance. Multi arterial bypass surgery comprises nearly 10% of the overall operations for ischemic heart disease. Multiple studies proved the superiority of arterial grafts for multivessel coronary artery disease. Nevertheless, the vast majority of conduits utilized for multiple bypasses are saphenous vein grafts. With the increasing popularity of radial artery utilization, the gastroepiploic artery remains a faded option. So more studies should be conducted for evaluation of the benefits from the gastroepiploic artery in the setting of the multi-arterial revascularization.

Objective. Presentation of approaches and operative techniques for complete arterial revascularization in patients with multivessel coronary artery disease.

Methods. Analytical review of literature on keywords in international scientometric databases Pub Med, Scopus, Web of Science. Search depth 12 years: from 2007 to 2018.

Results. Current paper presents operative techniques and approaches to complete arterial revascularization in patients with multivessel coronary artery disease. Internal mammary artery remains the "gold standard" for left anterior descending artery anastomosis site. Multiple arterial grafting is superior in terms of overall and cardiac survival. Emerging evidence of radial artery high term patency suggest the use of this arterial graft. Bilateral internal artery utilization provides long-term survival. Supplemental radial artery grafting to bilateral internal mammary provides complete arterial revascularization and can be safely used in routine cardiac surgery practice. Gastroepiploic artery proved superior patency rates, compared to saphenous vein grafts. Right coronary artery territory is ideal anastomotic site for gastroepiploic artery grafting. Inferior epigastric artery may be used in addition to others arterial grafts as free graft or as y- or t-graft in setting of multivessel coronary atherosclerotic lesions.

Conclusion. Complete arterial revascularization provides symptomatic relief from coronary artery disease provides superior patency rates and lowers incidence of major adverse cardiac events.

Key words: coronary artery bypass grafting, multivessel coronary disease, surgical revascularization, atherosclerosis, ischemic heart disease, radial artery, left internal mammary artery, right internal mammary artery, bilateral internal mammary artery, multiarterial coronary artery bypass grafting, gastroepiploic artery, inferior epigastric artery.

Relevance. Cardiovascular mortality in Ukraine remains the prevalent cause of death. Unpromising statistics of mortality from cardiovascular diseases illustrates the need for implementing effective treatment strategies and solutions. Coronary revascularization provides symptomatic relief from coronary artery disease and improves short and long-term outcomes.

Multi arterial bypass surgery comprises nearly 10% of the overall operations for ischemic heart disease. Multiple studies proved the superiority of arterial grafts for multivessel coronary artery disease. Nevertheless, the vast majority of conduits utilized for multiple bypasses are saphenous vein grafts. With the increasing popularity of radial artery utilization, the gastroepiploic artery remains a faded option. More studies should be conducted for evaluation of the benefits from the gastroepiploic artery in the setting of the multi-arterial revascularization.

Objective. Presentation of approaches and operative techniques for complete arterial revascularization in patients with multi-vessel coronary artery disease.

METHODS

Analytical review of literature on keywords in international scientometric databases Pub Med, Scopus, Web of Science. Search depth 12 years: from 2007 to 2018.

RESULTS AND DISCUSSION

Long-standing high-grade stenosis multivessel coronary artery disease eventually leads to heart failure with systolic dysfunction. Surgical revascularization may restore ejection fraction by elimination of myocardial hibernation. Despite common use of saphenous vein grafts, recent scientific publications recommends utilization of multiple arterial grafts in patients of all age groups [15]. Internal mammary artery (IMA) has patency rates in the region of 90-95% ten to fifteen years after CABG [16]. Based on superior long-term results of the internal mammary artery (IMA), other arteries are being used in CABG.

Complete arterial revascularization usually achieved using the following arterial grafts: left internal mammary artery (LIMA), right internal mammary artery (RIMA), bilateral internal mammary arteries (BIMA), radial artery (RA), gastroepiploic artery (GEA) and inferior epigastric artery (IEA) (Fig. 1). Multiple arterial grafts should be utilized in setting of diffuse varicose vein disease during complex cardiac surgery procedures, where PCI option

is failed, as well as ascending aorta calcification with diffuse atherosclerotic plaques. Different locations of arteries harvesting also have potential benefit in high-risk patients in terms of deep sternal wound infection (DSWI).

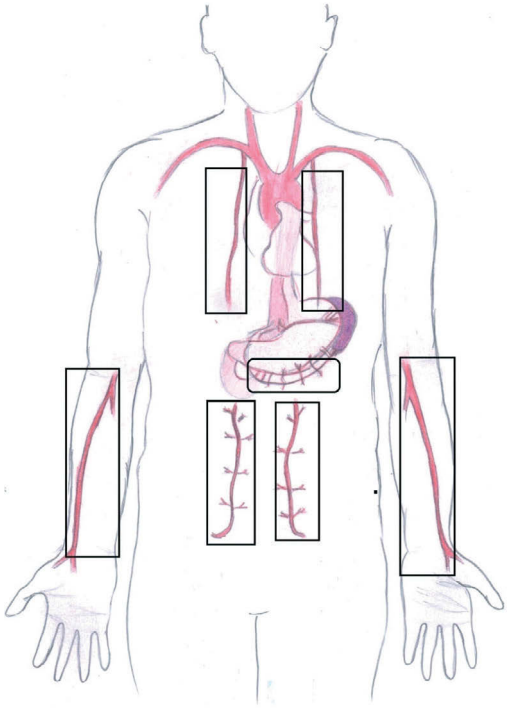

Fig. 1. Arteries commonly used for complete arterial revascularization

IMA harvesting technique:

Internal mammary artery (IMA) runs bilaterally from subclavian arteries medially to the anterior scalenus muscle and is accompanied by two veins. The free margin of IMA bifurcates at the level of sixth intercostal space into superior epigastric and musculophrenic arteries. The main blood supply to the sternum, derived from sternal and perforating branches of IMA. There are two techniques of IMA harvesting for CABG: pedicled and skeletonized. Dissection of the IMA as a pedicle includes harvesting with its surrounding fascia and both veins. It has been proposed that such preservation of its surrounding tissues provides a homeostatic milieu for the IMA, helping it retain its function once harvested [1]. The skeletonized technique was developed to preserve sternal perfusion and minimize trauma from pedicled IMA harvesting [4]. This involves dissection of the IMA from its accompanying venous drainage, innervation, lymphatics, muscle, and fascia from the top of the first rib to its bifurcation with branches of the IMA clipped and divided [2] (Fig. 2).

The wall of the IMA has the same 3 wall layer, which composed of intima, media and adventitia. It has a discontinuous internal elastic lamina and is less prone to spasm and arteriosclerosis [3]. Nitric oxide

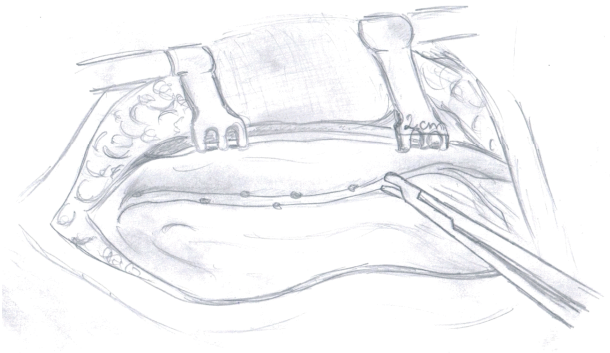

Fig. 2. Skeletonized left internal mammary artery with clipped perforating branches. Distal portion of IMA divides into superior epigastric and musculophrenic arteries

production is greater in the IMA than in the radial artery and long saphenous vein, and is associated with reduced smooth muscle proliferation, less intimal thickening, and improved long-term patency [4]. According to case-control study of 1526 patients, RIMA as a second conduit did not increase the operative risk including sternal wound complications and improved long term outcomes including overall survival when compared to RA [5]. The advantage of utilizing the RA in patients with diabetes mellitus and obesity in this cohort is straightforward. These findings strongly support RIMA as the first choice second arterial conduit in CABG [5].

Radial artery (RA) became important arterial conduit for coronary bypass grafting. Five-year patency rates in more recent studies are similar to IMA [18]. RA patency rates are superior to those of the saphenous vein grafts, particularly in the midterm and long term [6]. RA grafting has fewer major adverse events, similar patency to RITA, and improves survival in older and COPD patients [7]. Appropriate patient selection, coronary arteries target territory and high-grade stenosis are key parameters that influence RA patency rates.

RA harvesting technique

After collateral hand circulation assessment using modified Allen test a linear skin incision from the midpoint of elbow crease to the lateral margin of wrist crease is made. Skin incision line may be differentiated by palpating the radial pulse distally on the wrist and proximally by identifying aponeurosis of biceps brachii on the flexion. The fascia overlying the RA is incised distally as the RA emerges to become a subcutaneous structure. The fascia is divided more proximally with cautery, separating the muscle bellies of the brachioradialis muscle and the flexor carpi radialis muscle. Distally, the fascia is carefully divided with scissors due to the close proximity of the underlying RA [8]. There are two nerves that should be avoided during the RA harvest: the lateral antebrachial cutaneous nerve

and the superficial radial nerve. These nerves provide cutaneous innervation to the volar forearm, portions of the thumb and the dorsum of the hand [8]. Based on own experience RA harvesting with both veins that run along the artery is safer than skeletization (Fig. 3). Once the RA mobilized we apply clamp proximally for confirmation a retrograde flow from the ulnar artery supply, the vessel is ligated and transected. Similar actions provided to distal portion of RA. After the vessel is flushed with vasodilating solution, proximal and distal stumps are sewed with 5.0 polypropylene sutures. The arm is closed with cosmetic skin suture. Subcutaneous tissue and deeper fascia layers are left unapproximated to minimize the risk of compartment syndrome and nerve injury. Early career surgeons should be aware that patients with long-standing diabetes are prone to arterial calcification and occasionally, intraluminal calcium cannot be palpated during initial evaluation of RA graft.

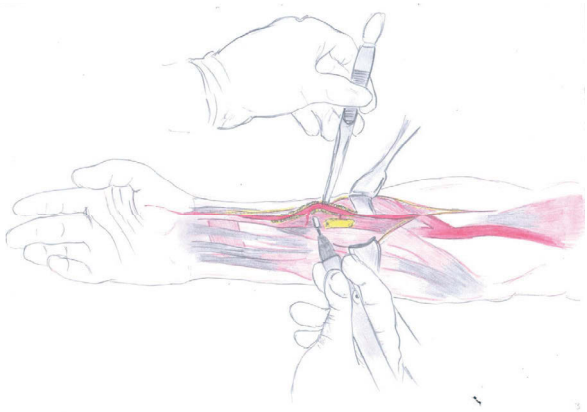

Fig. 3. Radial artery exposed and is harvesting with cautery

The right gastroepiploic artery (GEA) was used for indirect myocardial revascularization (Vineberg's procedure) for the posterior or inferior wall of the heart in the late 1960s by Bailey et al. [9] and its angiographic patency was demonstrated in 1969 by Hirose et al. With the development of coronary artery bypass grafting procedures, direct anastomosis of GEA to the right coronary artery was attempted by Sterling Edwards in early 1970s, but there was no exact documentation of the procedure. The GEA graft already has a 27-year history in CABG, and its clinical results are excellent, without an increase in perioperative risk. The reported cumulative patency rate of the GEA graft was 98.5% at 1 month, 93.7% at 1 year, 86.2% at 5 years, and 70.2% at 10 years [10].

Gastroepiploic artery harvesting technique

There are two gastroepiploic arteries: right and left:

- Left gastroepiploic arises from splenic artery;
- Right gastroepiploic artery, arises from gastroduodenal branch of proper hepatic artery.

It can be easily found between the layers of the greater omentum. For gastroepiploic artery harvesting the median sternotomy is extended just few centimeters below to the umbilicus with peritoneum opening. The part of stomach is delivered into the margin between thorax and abdomen by fenestrated atraumatic clamp, and the GEA is palpated along its greater curvature. GEA and surrounding tissue is detached from the greater curvature as a pedicled graft with no risk of subsequent gastric ischemia. GEA is delivered into the pericardial cavity by small incision in the diaphragm and is carefully placed on the anterior surface of the stomach (Fig. 4). The GEA is skeletonized and divided distally with intraluminal papaverine injection.

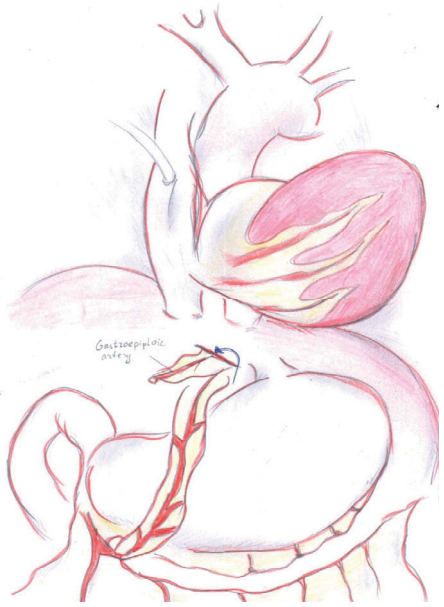

Fig. 4. GEA is detached from the greater curvature as a pedicled graft

Arterial grafts and target coronary arteries:

LIMA, RIMA patency are similar for most coronary artery territories. In setting of multivessel CAD: triple-vessel disease, with major stenosis in right coronary artery (RCA), left main coronary artery (left main LCA), proximal to distal left anterior descending artery (LAD), including diagonal branch and hemodynamically significant stenosis in the circumflex coronary artery (Cx) territory the following approaches may be recommended:

- LIMA – LAD, RIMA – RCA (including terminal divisions, if sufficient graft length, if insufficient - for distal RCA: RIMA may be anastomosed end – to end with RA), LIMA – RA (y- graft) – Cx. (Fig. 5)
- RIMA – LAD, RIMA – RA (y – graft) – RCA, LIMA – Cx.
- LIMA – LAD, GEA – RCA, LIMA – RIMA (y-graft) – Cx.
- LIMA – LAD, GEA – RCA, LIMA – IEA (y - graft) – Cx.
- RIMA – LAD, LIMA – Cx, aorta – RA (free graft) – RCA (Fig. 6)
- Aorta – RA – LAD, GEA – RCA, aorta – IEA – Cx.

- LIMA – LAD, LIMA – RIMA (y – graft) – Cx – RCA (sequential graft).
- LIMA – LAD, GEA – RCA, LIMA – RA (y – graft) – Cx.
- LIMA – LAD, LIMA – RA (proximal y- graft) to RCA and Cx (sequential, distal grafting)
- GEA – LAD, GEA – RA (y – graft) – RCA, GEA – RA (y – graft) – Cx.

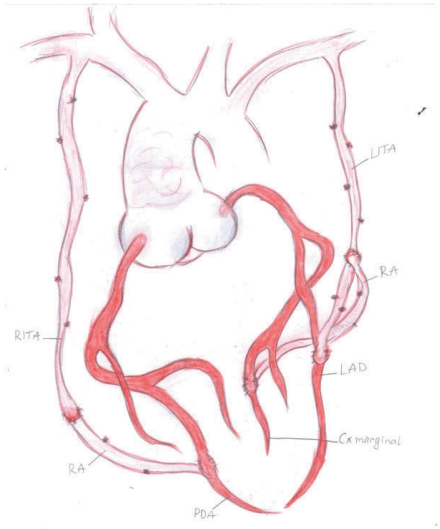

Fig. 5. Proposed method of revascularization in setting of triple-vessel CAD, right internal mammary artery anastomosed with posterior descending artery (RCA), using end to end anastomosis with radial artery; left internal mammary artery anastomosed with left anterior descending artery, radial artery anastomosed as y- graft with left internal mammary artery to obtuse marginal artery of Cx system.

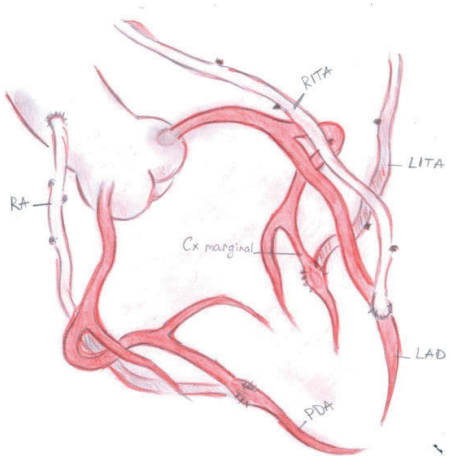

Fig. 6. Proposed method of revascularization in setting of triple-vessel CAD, right internal mammary artery anastomosed with left anterior descending artery; left internal mammary artery anastomosed with obtuse marginal artert of Cx system; radial artery anastomosed as free graft, proximally with aorta, distally with posterior descending artery (RCA).

Coronary revascularization in complex cardiac surgery procedures

In setting of complex cardiac surgery procedures (valve replacement/valve reconstruction, aortic procedures) and concomitant hemodynamically significant coronary artery stenosis, arterial grafting remains preferred option for revascularization [18]. Nevertheless, high grade stenosis for RCA > 90 % and for left-main with major distributions of LCA > 70% of stenosis are the key parameters for long-term arterial graft patency.

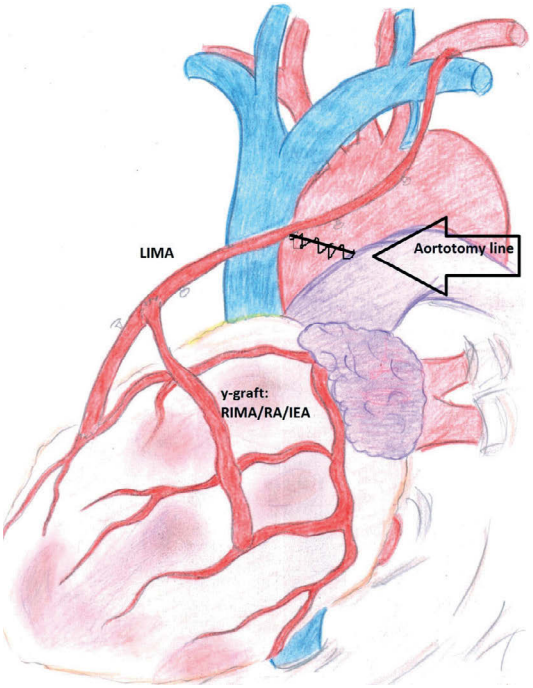

Fig. 7. Proposed method of revascularization in complex cardiac surgery procedures: aortic valve replacement with high-grade stenosis of left-main coronary artery: left internal mammary artery anastomosed with left anterior descending artery, for arterial y-graft, the following arteries may be utilized: right internal mammary artery/ radial artery/inferior epigastric artery anastamosed with obtuse marginal artery of Cx system

Pharmacological agents used for spasm prevention

Many surgeons are reluctant utilizing multiple arterial grafts in their routine practice for higher harvesting precision, longer duration and properties of arterial grafts, which are prone to spasm. However, there are numerous pharmacologic agents, used for this particular issue. All pharmacologic vasodilator drugs relax the vessel through specific mechanisms, and therefore, there is no perfect, single best vasodilator to prevent or treat spasm of the arterial graft against all mechanisms of contraction [14]. The standard papaverine solution, used for spasm prevention, may be supplemented by calcium channel blockers – verapamil. Decision on intraluminal injection or gentle external irrigation left for surgeon

competency. However free grafts, such as RA, GEA and IEA are highly recommended for intraluminal injection for resting blood flushing. Phosphodiesterase inhibitors – milrinone, are highly effective in spasm prevention [19]. According to own experience, patients who underwent complete arterial revascularization should receive calcium – channel blockers (dosage, calculated according to patient's blood pressure) on the first postoperative day and subsequently next six month after operation.

CONCLUSIONS

The superiority of arterial grafts for myocardial revascularization led surgeons to commonly use both internal thoracic arteries and increasingly frequent use the gastroepiploic artery to graft (reach) coronary arteries on the inferior ventricular wall. The radial artery has been assuming an increasingly prominent role in arterial revascularization, often being used when additional arterial conduits are desired in conjunction with the internal mammary arteries. Inferior epigastric artery graft is good alternative arterial graft for patients, who previously underwent chest radiotherapy or blunt thoracic trauma. IEA graft may serve as a complement of the myocardial revascularization in patients over 70 years old for better clinical results because of intact IMAs without comprising sternal blood supply. Preferential non aortic (no – touch aorta) manipulation is highly recommended, however there are no statistically significant data on risk in long-term results of such method.

Complete arterial revascularization provides symptomatic relief from coronary artery disease provides superior patency rates and lowers incidence of major adverse cardiac events.

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ПОВНА АРТЕРІАЛЬНА РЕВАСКУЛЯРИЗАЦІЯ МІОКАРДУ: ОПЕРАТИВНІ ПРИЙОМИ У ПАЦІЄНТІВ З МУЛЬТИСУДИННИМ УРАЖЕННЯМ КОРОНАРНИХ АРТЕРІЙ. Огляд

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Актуальність. Мультиартеріальне шунтування складає майже 10% загальних операцій при ішемічній хворобі серця. Мультицентрові дослідження довели перевагу артеріальних трансплантатів при мультисудинному ураженні коронарних артерій. Тим не менше, переважна більшість шунтів, що використовуються при операції шунтування коронарних артерій, є трансплантатами підшкірних вен. Зі збільшенням популярності використання променевої артерії артерія gastroepiploica залишається невизначеним варіантом. Саме тому необхідно провести більше досліджень для оцінки переваг артерії gastroepiploica при мультиартеріальній реваскуляризації.

Мета: презентація підходів та оперативних методів для повної артеріальної реваскуляризації у хворих з мультисудинним ураженням коронарних артерій.

Методи. Аналітичний огляд літератури за ключовими словами у міжнародних наукометричних базах Pub Med, Scopus, Web of Science. Глибина пошуку 12 років: з 2007 р. до 2018 р.

Результати. У даній роботі представлені методи виділення артеріальних кондуїтів та підходи до повної артеріальної реваскуляризації у хворих при мультисудинному враженні коронарних артерій. Внутрішня грудна артерія залишається «золотим стандартом» для анастомозу з передньою міжшлуночковою гілкою лівої коронарної артерії. У пацієнтів молодого віку рекомендується мультиартеріальне шунтування. Останні літературні дані вказують на високі показники прохідності променевої артерії. Білатеральне використання внутрішніх грудних артерій забезпечує тривалий термін життя пацієнтів після коронарного шунтування. Використання променевої артерії, у- або t-графтом, доповнене білатеральними внутрішніми грудними артеріями, забезпечить повну артеріальну реваскуляризацію і може бути безпечно використано в рутинній практиці серцево-судинної хірургії. Arteria gastroepiploica має вищі показники прохідності, порівняно з аутовенозними трансплантатами. Територія правої коронарної артерії є ідеальним місцем анастомозу для шунтування артерією gastroepiploica. Arteria epigastrica inferior може бути використана в додаток до інших артеріальних трансплантатів у вигляді вільного трансплантата або як у- або t-графта при мультисудинних коронарних атеросклеротичних ураженнях.

Висновок: повна артеріальна реваскуляризація міокарду, окрім усунення симптомів ішемічної хвороби серця, забезпечує тривалий час функціонування шунтів, а також знижує частоту значних серцевих ускладнень.

Ключові слова: аортокоронарне шунтування, мультисудинна ураження коронарних артерій, хірургічна реваскуляризація, атеросклероз, ішемічна хвороба серця, променева артерія, ліва внутрішня грудна артерія, *arteria gastroepiploica, arteria epigastrica inferior*

ПОЛНАЯ АРТЕРИАЛЬНАЯ РЕВАСКУЛЯРИЗАЦИИ МИОКАРДА: ОПЕРАТИВНЫЕ ПРИЕМА У ПАЦИЕНТОВ С МУЛЬТИСОСУДИСТЫМ ПОРАЖЕНИЕМ КОРОНАРНЫХ АРТЕРИЙ. Обзор

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Актуальность. Мультиартериальное шунтирование составляет почти 10% общих операций при ишемической болезни сердца. Мультицентровые исследования доказали преимущество артериальных трансплантатов при мультисосудистом поражении коронарных артерий. Тем не менее, подавляющее большинство шунтов, используемых при операции шунтирования коронарных артерий, является трансплантатами подкожных вен. С увеличением популярности использования лучевой артерии артерия gastroepiploica остается неопределенным вариантом. Поэтому необходимо провести больше исследований для оценки преимуществ артерии gastroepiploica при мультиартериальной реваскуляризации.

Цель: презентация подходов и оперативных методов для полной артериальной реваскуляризации у больных с мультисосудистым поражением коронарных артерий.

Методы. Аналитический обзор литературы по ключевым словам в международных наукометрических базах Pub Med, Scopus, Web of Science. Глубина поиска 12 лет: с 2007 г. до 2018 г.

Результаты. В данной работе представлены методы выделения веществ артериальных кондуитов и подходы к полной артериальной реваскуляризации у больных при мультисосудистом поражении коронарных артерий. Внутренняя грудная артерия остается «золотым стандартом» для анастомоза с передней межжелудочковой ветвью левой коронарной артерии. У пациентов молодого возраста рекомендуется мультиартериальное шунтирование. Последние литературные данные указывают на высокие показатели проходимости лучевой артерии. Билатеральное использование внутренних грудных артерий обеспечивает длительный срок жизни пациентов после коронарного шунтирования. Использование лучевой артерии, y- либо t-графт, дополненное билатеральными внутренними грудными артериями, обеспечит полную артериальную реваскуляризацию и может быть безопасно использовано в рутинной практике сердечно-сосудистой хирургии. Arteria gastroepiploica имеет высокие показатели проходимости по сравнению с аутовенозными трансплантатами. Территория правой коронарной артерии является идеальным местом анастомоза для шунтирования артерией gastroepiploica. Arteria epigastrica inferior может быть использована в дополнение к другим артериальным трансплантатам в виде свободного трансплантата или как y- или t-графты при мультисосудистых коронарных атеросклеротических поражениях.

Вывод: полная артериальная реваскуляризация миокарда, кроме устранения симптомов ишемической болезни сердца, обеспечивает длительное время функционирования шунтов, а также снижает частоту значительных сердечных осложнений.

Ключевые слова: аортокоронарное шунтирование, мультисосудистые поражения коронарных артерий, хирургическая реваскуляризация, атеросклероз, ишемическая болезнь сердца, лучевая артерия, левая внутренняя грудная артерия, *arteria gastroepiploica, arteria epigastrica inferior*

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EXPERIENCE IN PERFORMING PUNCTURE AND DRAINAGE MINI-INVASIVE INTERVENTIONS UNDER ULTRASOUND CONTROL IN THE DIAGNOSIS AND TREATMENT OF ABDOMINAL DISEASES AND POSTOPERATIVE COMPLICATIONS. Review

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Resume. The article presents a description of the main puncture and drainage interventions, indicating the method of their implementation, techniques, materials used for their implementation. The own experience of application of the specified minimally invasive interventions in treatment of a syndrome of mechanical jaundice of benign and malignant genesis, acute cholecystitis, acute pancreatitis and its complications, hepatic abscesses, limited liquid accumulations of an abdominal cavity and retroperitoneal space is described. The advantages and disadvantages are noted, a comparative assessment is made and recommendations are given for the use of different puncture and drainage interventions depending on the type of pathology in which they are used.

Keywords: mechanical jaundice, endobiliary interventions, percutaneous-transhepatic cholangiostomy, percutaneous-transhepatic cholecystostomy, postoperative fluid accumulations.

An important achievement of the twentieth century was the widespread introduction of new technologies in medicine, including surgery. Traditional operations have been replaced by minimally invasive minimally invasive laparoscopic, X-ray endovascular, endoscopic and percutaneous interventions, which can significantly affect the results of treatment of a wide range of surgical diseases [6, 7]. The combination of ultrasound imaging with invasive interventions has been called ultrasound diapeutics in the scientific literature. It took years to overcome the traditionally conservative psychology of surgeons to achieve recognition of the effectiveness of puncture-drainage invasions of the biliary tract, limited fluid and purulent foci of the liver, pancreas and abdomen under ultrasound control [10, 11].

Most invasive percutaneous interventions are performed under the control of ultrasonic devices equipped with convex and linear sensors 3.5 MHz - 5 MHz, using puncture nozzles or the method of «free hand» (free hand method) and are used mainly for punctures and drainage of large demarcated fluid cavity, pleural cavities, liver biopsy, percutaneous endobiliary interventions [11, 13].

An important advantage of ultrasound-guided percutaneous interventions over X-ray-controlled interventions is the absence of significant radiation exposure to the patient and medical staff, as well as the possibility of dynamic monitoring of the patient.

Invasive interventions on the technique of execution are divided into punctures and drainage, which, in turn, is divided into two-moment and one-moment. Two-stage drainage includes drainage according to Seldinger's method, one-stage drainage includes stiletto catheter drainage and trocar method.

For punctures flexible needles of various design, 15-25 centimeters long, with a diameter of 16-23 g (1,6-0,6 mm) are used. The choice of design, diameter and length of the needle depends on the purpose and intended depth of the puncture. The flexibility and fineness of the needle allow you to puncture organs that are in physiological motion without any significant risk of damage. Needles with diameters of 16-19 g (1.6-1.1 mm) are used for punctures of liquid formations. For this purpose, Chibs needles are most often used, which are a hollow structure, ultrasonic visualization of which is achieved by the presence of a mixture of air, liquid and tissues in its lumen. Its tip is visualized as a single echo. All invasive interventions are performed under local anesthesia in accordance with the rules of asepsis and antiseptics, less often (in children and restless patients) - under short-term intravenous anesthesia [5, 7, 8].

Various modifications of X-ray contrast catheters are used for percutaneous drainage, most often with the help of outer diameters of lumens 5-15 F on the Charrier scale (corresponds to 1.7-5.0 mm), approximately on the type of «pigtail» with white holes; catheter styles are used for one-stage drainage (Fig. 1). The drainage kit also includes angiographic flexible conductors of various diameters, up to 70 centimeters long (straight and J-type) and soft plastic dilators with a central channel of increasing diameter (7-10 F) to expand the lumen of the channel to the required drainage. Nowadays, disposable sterile kits

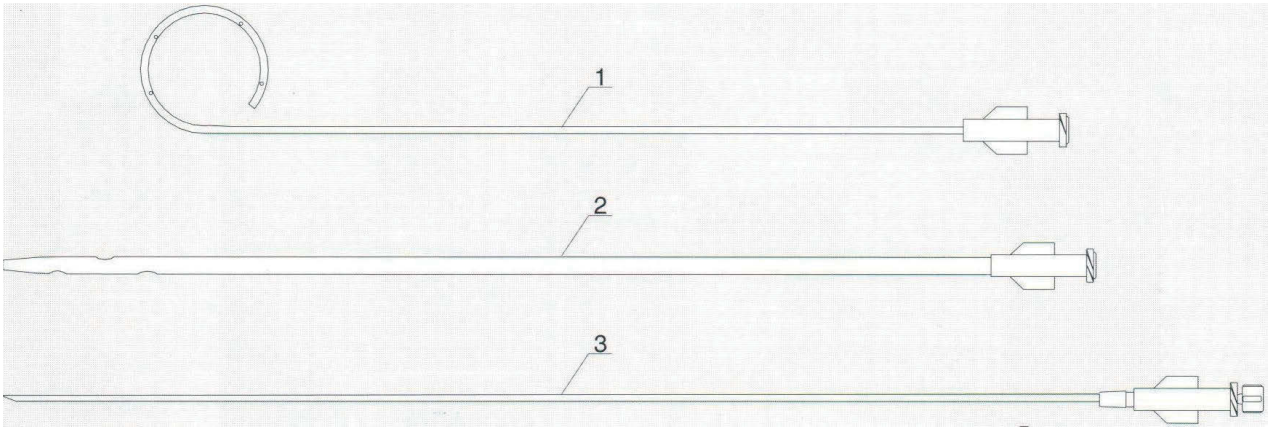


Fig. 1. Set for a through catheter (1 - a catheter like Pigtail, 2 - a direct catheter, 3 - a two-component needle).

(needle, conductor, drainage, additional accessories) of various foreign manufacturers (Cook, Somatex, Balton, etc.) are widely used [6, 7].

For the endoprosthesis of the biliary tract uses a set developed by prof. Ivshin VG (Fig. 2), as well as metal mesh braided stents with Wallstent memory with Permalume coating (without WallFlex coating) and delivery system Unistep Plus (Boston Scientific, USA) and Hanarostent Biliary Non-covered, Shim-Hanarostent covered and Hanarostent Biliary

Hilar (MI Tech, Korea) complete with a delivery device with a diameter of 8-10 mm, a length of 50-120 mm (Fig. 3).

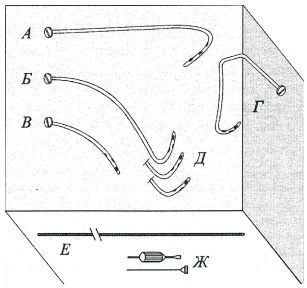


Fig. 2. Set for endoprosthesis of bile ducts (A, B, C, D - endoprosthesis for the right lobe of the liver; D - endoprosthesis for the left lobe of the liver; E - angiographic flexible conductor; F - screwdriver)

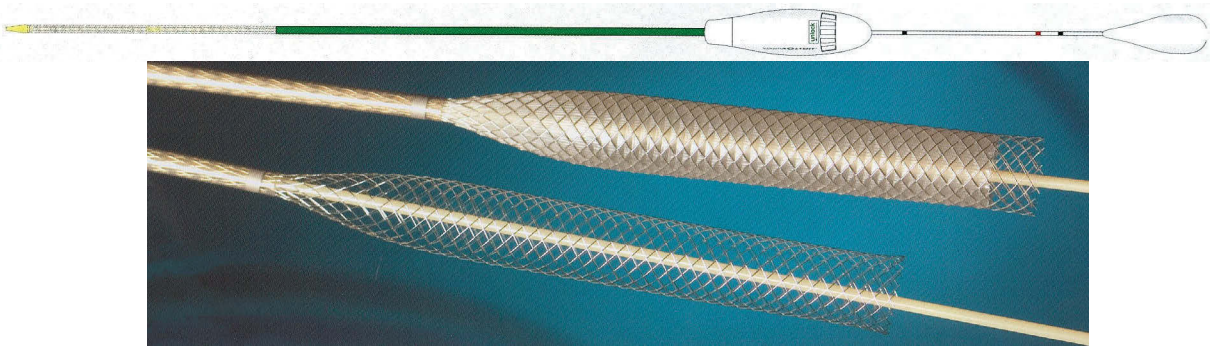


Fig. 3. Set for endobiliary stenting Hanarostent Biliary (M.I. Tech, Korea) and kit for endobiliary stenting Wallstent (Boston Scientific, USA)

Preparation of patients is carried out according to the generally accepted method for ultrasound examinations. Punctures are performed in the position of the patient on his back or side in accordance with the rules of asepsis under local anesthesia.

The contents obtained by puncture or drainage are subject to cytological, biochemical, bacteriological examination, determination of sensitivity to antibiotics, etc.

In recent decades, in most industrialized countries of the world there has been a steady increase in the incidence and prevalence of gallstones, especially its complicated forms (choledocholithiasis, mechanical jaundice, acute cholecystitis, purulent cholangitis, stricture of the terminal duodenal cholecystitis etc.), damage and strictures of the bile ducts, benign and malignant tumors of the pancreas, duodenum, bile ducts, liver, etc., which usually also cause obstruction of the biliary tract with the development of mechanical jaundice, purulent cholangitis and other complications (in 20.1- 80.5% of patients with choledocholithiasis, 30-50% - with tumor lesions of the

hepatopancreatoduodenal area, 50-7.20% - with strictures of the extrahepatic bile ducts, etc.) [1, 2, 6, 8].

Mechanical jaundice - is a symptom complex caused by disruption of the natural passage of bile due to obstruction of the biliary tract of benign or tumor origin, which results in cholestasis, biliary hypertension, microcirculation disorders, dystrophy and focal necrosis in the liver parenchyma leading to liver failure. , barrier, synthetic and other liver functions, as well as progressive toxemia due to the entry of toxic products of bile breakdown into the systemic bloodstream, microbial contamination and translocation of intestinal microflora into the portal system with the subsequent implementation of multiorgan failure syndrome, which is one of the most common causes of death [6].

In 23.4-50.1% of patients with MJ (Mechanical Jaundice) is accompanied by purulent cholangitis, which is a consequence of prolonged cholestasis. Given the real threat of the spread of the inflammatory process to numerous, even the smallest bile ducts, acute cholangitis can be manifested by a septic condition, which in biliary hypertension often causes the development of intrahepatic cholangiogenic abscesses, biliary sepsis, resulting in high mortality, resulting in high mortality. data from various authors, in the range of 12.1-31.3%. Its main cause in this category of patients is progressive liver and kidney failure [6, 14].

With complete biliary obstruction of any genesis, rapidly progressing intraductal hypertension is accompanied by the rapid development of endotoxemia, purulent cholangitis, biliary sepsis, bacterial-toxic shock, progressive hepato-renal failure, which necessitates the urgent implementation of surgical with serious metabolic disorders in 50% or more causes death [13, 14, 16].

Today, according to most leading biliary surgeons in the world, the method of choice in the surgical treatment of patients with MJ (Mechanical Jaundice) benign and tumor origin is a two-stage surgical tactic, which involves performing in the first stage of decompression of the biliary tract one of the minimally invasive (endoscopic retrograde or transdermal) in combination with active conservative therapy, and at the II stage - radical surgical intervention aimed at eliminating the main cause of biliary hypertension.

Decompression of the biliary tract is the most important stage in the treatment of severe forms of MJ (Mechanical Jaundice). The nature of the main disease of the Hepatoduodenal area, which led to the development of MJ (Mechanical Jaundice), and its location are crucial in choosing the method and method of restoring bile passage, the arsenal of which in recent decades, especially with the introduction of endoscopic and antegrade endobiliary technology has increased significantly.

Since the mid-1970s, endoscopic retrograde interventions have taken the leading place in the diagnosis and treatment of choledocholithiasis, primarily endoscopic retrograde cholecystopancreatography with endoscopic papillosphincterotomy (over 30 years). For the first time this method of minimally invasive biliary decompression, independently of each other, was performed in 1974 in Germany by M.Classen and L.Demling, as well as in Japan by K.Kawai and co-workers. This low-trauma, highly effective and relatively close to physiological intervention quickly became widespread in most of the world's leading surgical clinics. In recent decades, in order to decompress the biliary tract and eliminate biliary hypertension, it is performed in 72.4-85.2% of patients with MJ (Mechanical Jaundice) due to choledocholithiasis, limited strictures of the terminal choledochus, duodenum, chronic indurative pancreatitis and more. However, the use of this technique is limited by high rates of complications and mortality, which are 3.3-8.8% and 0.4-1.3%, respectively. The most severe of them are bleeding from papillotomy (1.4-4.0%), the development of acute cholangitis, pancreatitis (0.9-6.3%), perforation of the duodenum (0.2-0.5%), requiring immediate open surgery to correct complications and others [3, 6, 7].

At the present stage of development of biliary surgery, among the various methods of biliary decompression, one of the leading places is beginning to be occupied through skin and transhepatic techniques of reproduction of the biliary tract under ultrasound control. Among them, the most common is due to cutaneous-hepatic cholangiostomy, the results are shown in MJ (Mechanical Jaundice) with high and medium registration of bile flow (choledocholithiasis, strictures, training and tumors of the main bile ducts, duodenum, pancreas, etc.).

Performing cutaneous-hepatic cholangiostomy is a priority in cicatricial stricture of the distal choledochus in combination with purulent cholangitis, which allows for antegrade rehabilitation of bile ducts and their preparation for subsequent dilatation of the stricture, endoprosthesis or stenting [7, 9, 10]. Increasingly common in biliary surgery for MJ (Mechanical Jaundice), acute cholecystitis is cutaneous-hepatic cholangiostomy for biliary decompression, as well as rehabilitation of the gallbladder in patients with extremely severe somatic condition, which becomes an obstacle to more complex surgery [12, 15, 16, 17] (Fig. 5).

Antegrade percutaneous-transhepatic endobiliary interventions are a set of minimally invasive techniques, each of which involves solving a specific diagnostic or therapeutic goal, and their use in various combinations - to eliminate MJ (Mechanical Jaundice) and prepare for palliative or radical treatment of patients, and may be the final method of treatment inoperable patients with malignant lesions of the hepatopancreatoduodenal area.

These techniques differ favorably from open surgical interventions with laparotomy access with low trauma, lower incidence of complications. The use of antegrade endobiliary interventions makes it possible to perform cholangiography, which allows to determine the level, length and nature of obstruction of the biliary tract.

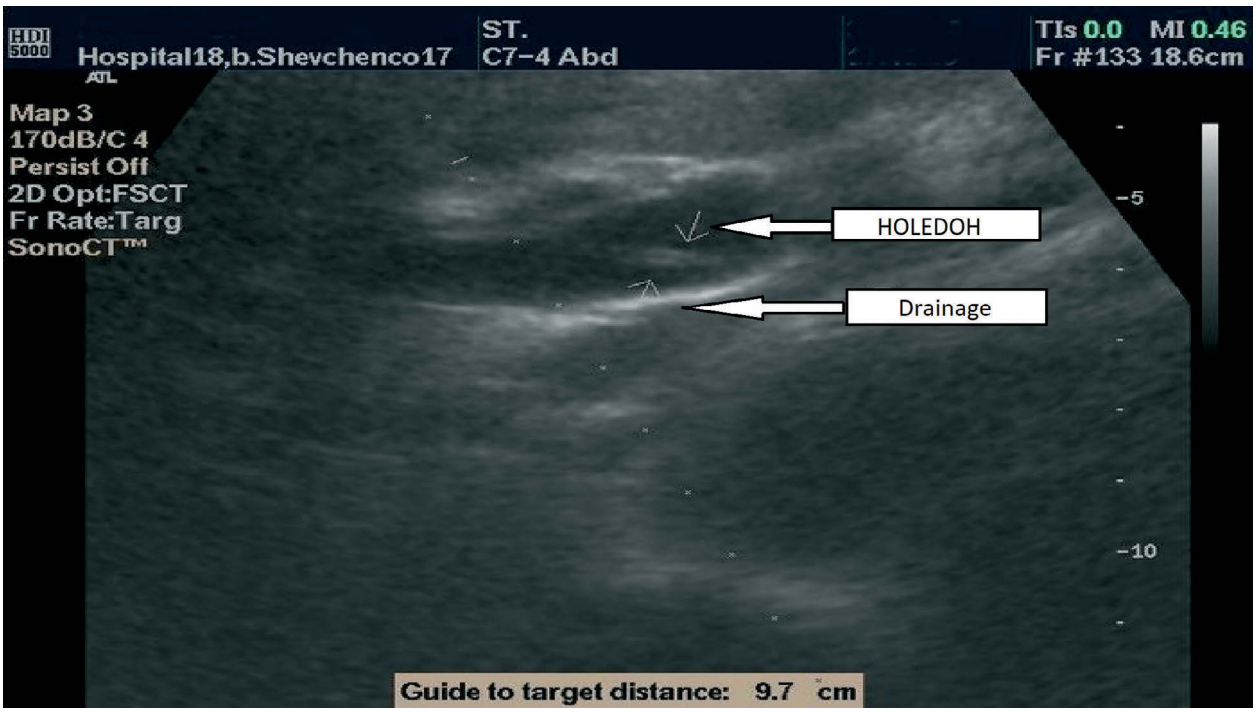


Fig. 4. Percutaneous-transhepatic cholangiostostomy under ultrasound control

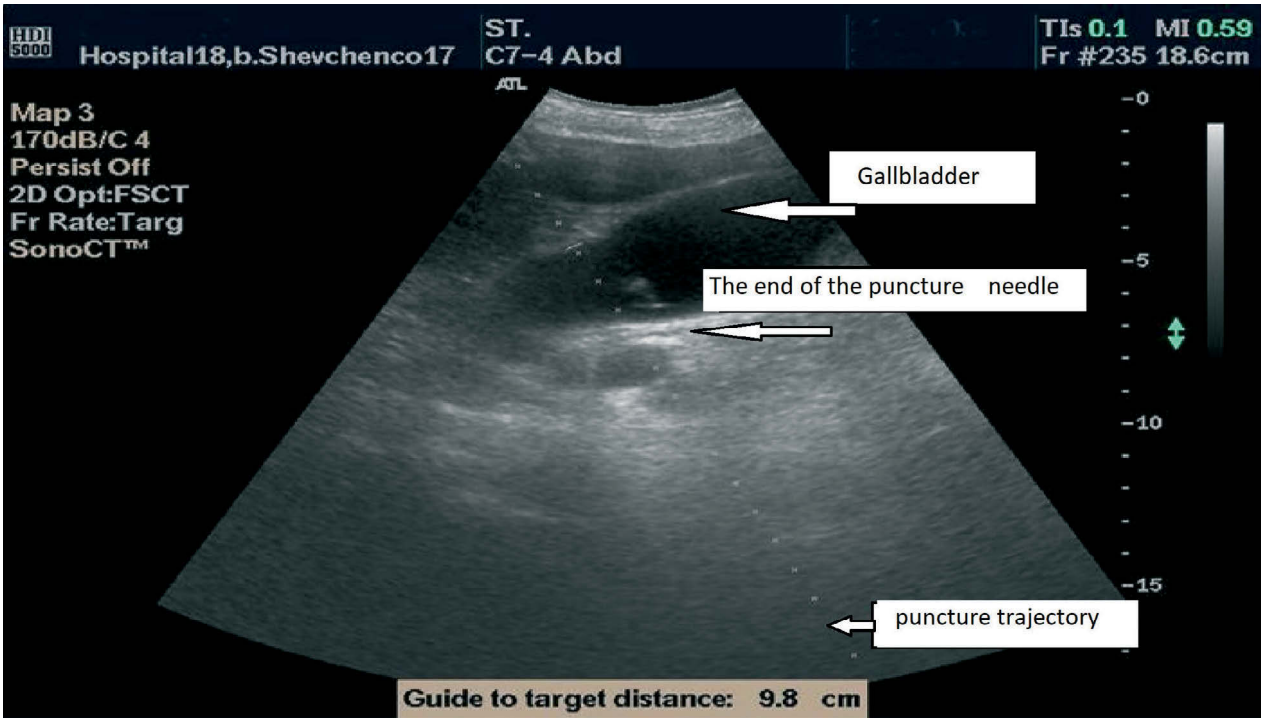


Fig. 5. Percutaneous-transhepatic cholecystostomy under ultrasound control

Therefore, endobiliary puncture interventions are divided into diagnostic and therapeutic, among which there are:

1. Percutaneous-transhepatic puncture cholangiography;
2. Multivariate percutaneous-transhepatic cholangiostomy;
3. Percutaneous-transhepatic cholecystostomy;
4. Antegrade bile duct endoprosthesis;
5. Antegrade stenting of the bile ducts.

Depending on the direction of bile drainage (outside or in the lumen of the gastrointestinal tract) after the intervention, as well as taking into account the time interval (duration) - simultaneously or delayed, there are:

1. External drainage.
2. One-time internal drainage.
3. Delayed internal drainage.

Performing percutaneous-transhepatic cholecystostomy under ultrasound control, according to most biliary surgeons, is a priority in the localization of the biliary block distal to the confluence of the gallbladder into the common bile, provided that the patency of the first of them under the following conditions (Fig. 6.):

- with slight dilatation of the bile ducts, which complicates the performance of percutaneous-hepatic cholangiostostomy;
- with a significant increase in the size of the gallbladder;
- with a perfect fit of the gallbladder to the lower surface of the liver.

The method of performing percutaneous-transhepatic cholecystostomy under ultrasound control, which is successful in the vast majority of patients, is a simple and minimally traumatic method of biliary tract drainage, which can be effectively used in inoperable patients with MJ at high risk of any other surgery to provide temporary or permanent decompression of the biliary tract.

In patients with MJ (Mechanical Jaundice) tumor origin, which is due to different in nature and prevalence of malignant neoplasms, the tactics of antegrade endobiliary interventions involve achieving biliary decompression during the preparation of the patient for radical or palliative surgery (or may be the final method of treatment).

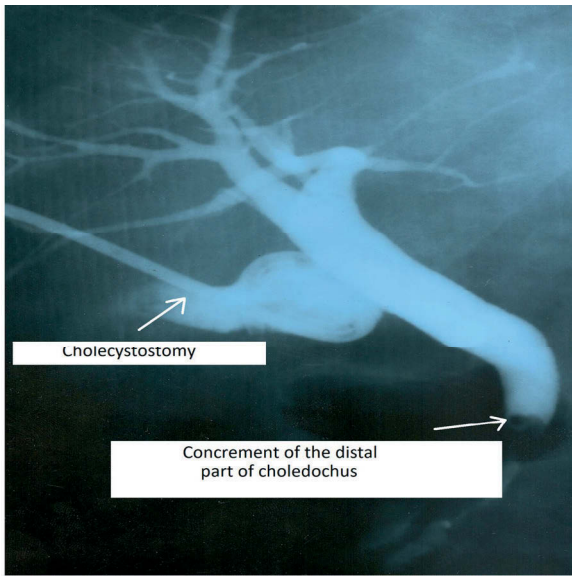


Fig. 6. Percutaneous-transhepatic cholecystostomy, fistulography. Choledocholithiasis, a stone of the distal choledochus

Irrespective of the reasons which have caused MJ (Mechanical Jaundice), medical tactics usually assume performance of antegrade external drainage (ED) of bilious channels. After achieving biliary decompression, the mode of ED can be switched to the mode of internal drainage (ID). In 1978, F. Burcharth proposed a method of transpapillary antegrade endoprosthesis, and subsequently introduced endobiliary ante- and retrograde

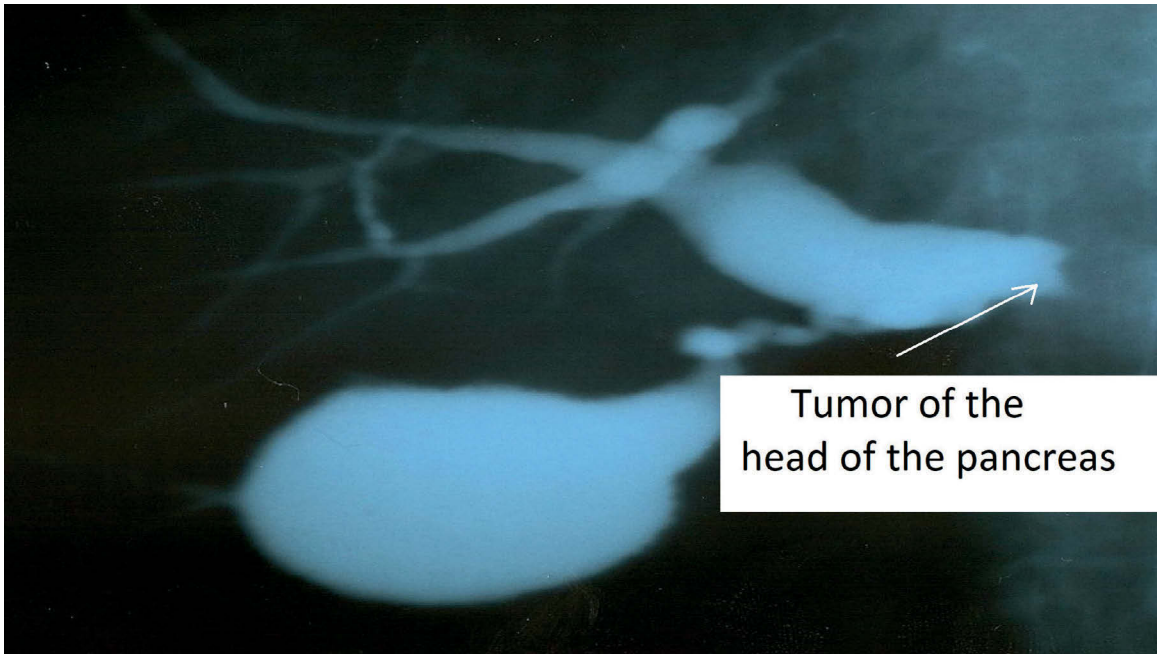


Fig. 7. Percutaneous-transhepatic cholecystostomy, fistulography. Cancer of the head of the pancreas with a block at the level of the upper third of the choledochus

prosthesis of the bile ducts under X-ray television, ultrasound or choledochoscopic control.

Biliary prostheses are a segment of a polymer tube made of synthetic materials - Teflon, polyurethane and other materials of sufficient length to restore the passage of bile into the duodenum from the part of the choledochus, which is above the site of obstruction. Teflon and polyurethane endoprostheses have better characteristics (better slip, inlay resistance, etc.).

Endoprosthesis (EP) of the bile ducts is performed in order to restore the natural passage of bile in the gastrointestinal tract, eliminate the inconvenience of catheter drainage and improve the quality of life of the patient (Fig. 8).

Indications for EP are:

1. predicted life expectancy of patients with malignant tumors of the biliopancreatoduodenal area, not more than 6 months;
2. old age, and / or exhaustion, and / or severe condition of the patient;
3. complete pathomorphosis of a malignant tumor after radiation therapy or combination therapy.

Endoprosthesis has a number of advantages over external drainage of the biliary tract:

- no risk of complications, educational injections of the proximal end of the drainage of the external (pain, infection of the wound at the injection and fixation of drainage, bile infection and the development of cholangitis, dislocation or accidental removal of drainage of another);
- no need for daily repeated inspection for drainage and the place of its introduction;
- lack of negative psychological impact on the patient by reminding him of the presence of permanent drainage, serious illness and future surgery;
- ensuring a more efficient digestive process by restoring the physiological passage of bile into the duodenum.

The accumulated experience in the use of antegrade endoprosthetics and stenting of the biliary tract indicates their high efficiency as a method of restoring bile outflow in MJ of benign and tumor origin. In some cases, arthroplasty is an alternative to palliative surgery, which is especially important for elderly and senile patients with metastatic cancer of the pancreas, duodenum, etc.

Antegrade decompression of the bile ducts allows to eliminate cholemia in 90% of patients, exceeds the results of the surgical method in terms of complications, mortality, life expectancy, reduces the patient's stay in the hospital. Until recently, mortality from complications of interventional drainage of the bile ducts reached 20-30% of cases, in recent years did not exceed 3-4.2%, which was made possible by improving the technique of interventions and the quality of postoperative care.

Thus, in wide clinical practice today many effective methods of antegrade decompression of a biliary tract at MJ (Mechanical Jaundice) of any genesis are widely enough used.

Among the problems of emergency surgery of the abdominal cavity, one of the leading places is acute cholecystitis (AC), which is second only to acute appendicitis. Its frequency, at present, reaches 17-18% of all cases of diseases of the abdominal cavity, which necessitate emergency surgery [16, 17]. About 40% of such patients are people older than 60 years. Although today the algorithm of surgical tactics in the treatment of this pathology is clearly defined, which provides priority for cholecystectomy, the question of determining the amount of primary surgery in elderly and senile patients with severe comorbidities, which causes the progression of the syndrome of mutual burden significantly increases the operational and anesthetic risk [14, 18]. The situation is complicated by the rapid increase in destructive changes in the gallbladder, which further exacerbates the already serious condition of patients. Effective in such cases is the decompression of the biliary tract due to percutaneous-transhepatic cholecystostomy in patients with preserved patency of the vesical duct (Fig. 9).

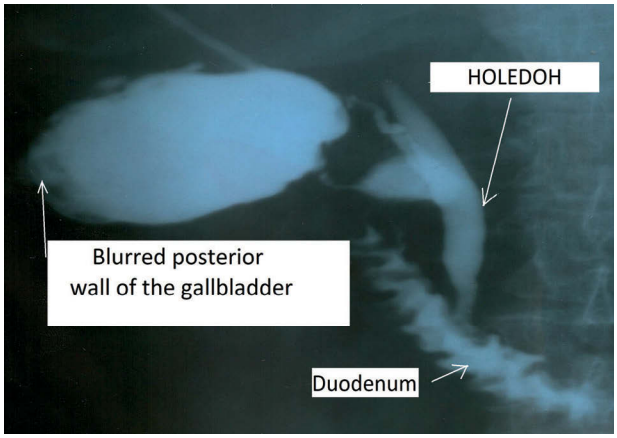
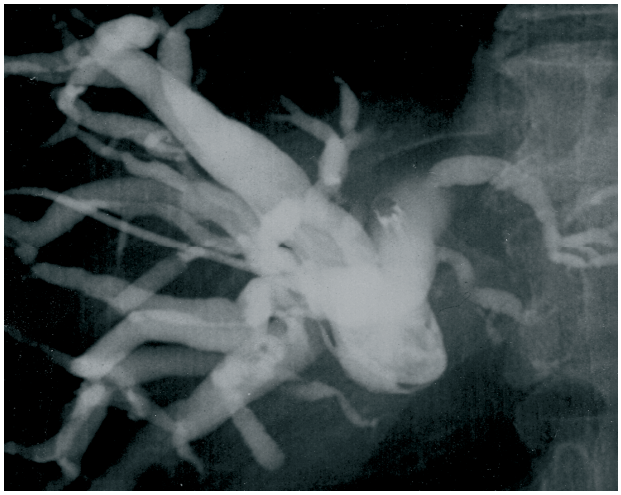


Fig. 9. Microcholecystostomy in a patient with acute calculous cholecystitis, gallbladder empyema

Most intensively, in recent years, percutaneous interventions in combination with video laparoscopic and other minimally invasive interventions are used in the treatment of complications of acute destructive pancreatitis, dramatically changing the situation in the tactics of management and treatment of this pathology.

Acute pancreatitis is one of the most severe in the clinical course and consequences of surgical diseases of the abdominal cavity, which is still accompanied by high mortality (25-41%), which does not tend to decrease due to the complexity of pathogenesis, difficulties in diagnosis and treatment. 18% of patients with acute destructive pancreatitis develop phlegmon of the retroperitoneal space, 10% - pseudocyst of the pancreas, 5% have bleeding into the cavity of the omental sac with the formation of hematomas, 1-9% - an abscess is



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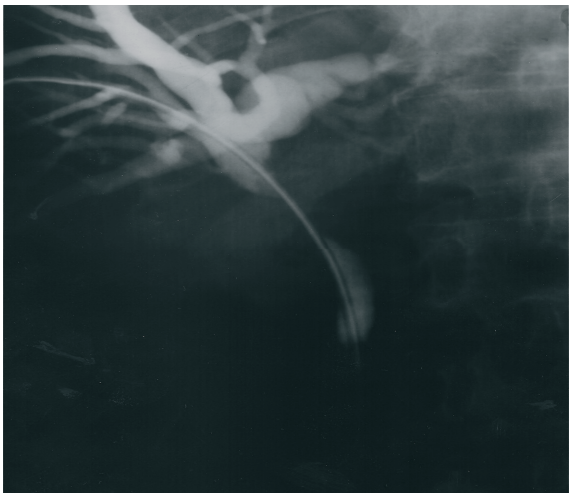

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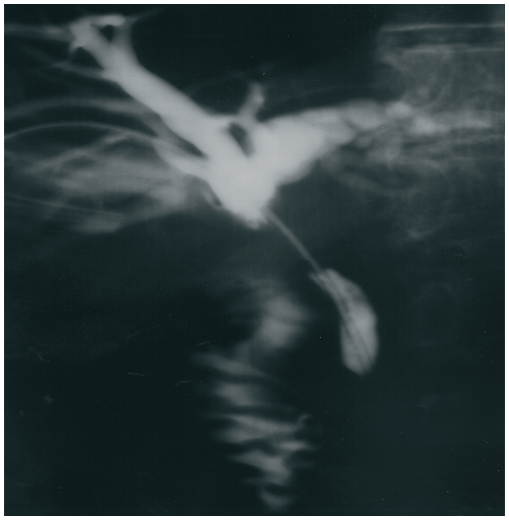

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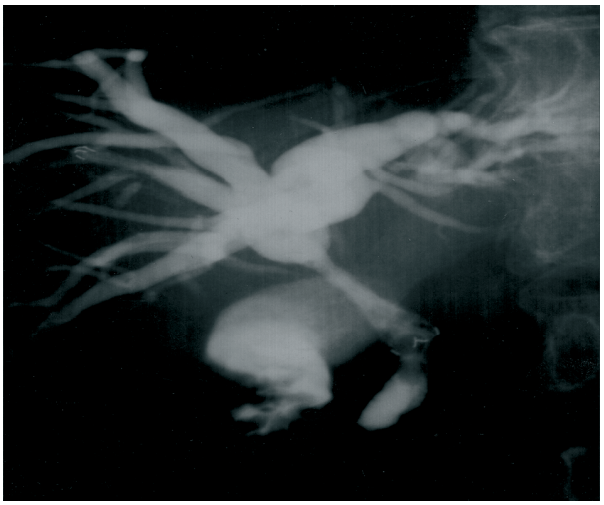

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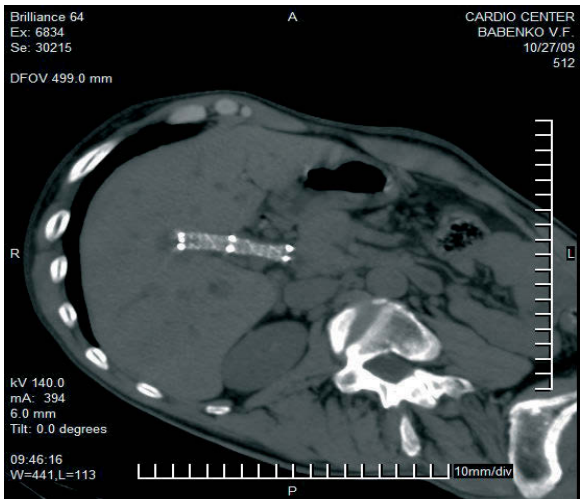

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Fig. 8. Stages of antegrade endobiliary stenting in a patient with Klatskin's tumor (1 - percutaneous-transhepatic cholangiostomy; 2 - tumor recanalization; 3 - delayed external-internal drainage; 4 - stent installed in the common hepatic duct; 5 - computed tomography after 2 months after stenting)

formed. Crucial in the treatment of this pathology is the timely implementation of adequate surgery [4, 8, 10, 11]. However, today there is no single concept in determining the timing and scope. Most researchers are inclined to think about the ineffectiveness of early laparotomies, which in most cases usually end in simple drainage of the omental sac, abdominal cavity and retroperitoneal space. On the other hand, the rapid development of endogenous intoxication syndrome and, as a consequence, the threat of such a formidable complication as multiple organ failure, force the surgeon to perform surgery with a significant risk to the patient's life. Based on the above, a possible way to solve this problem, in parallel with intensive care, is to perform percutaneous minimally invasive interventions under ultrasound control, which can mostly ensure the aseptic nature of pancreatic necrosis, reduce the possibility of bacterial translocation to the destruction zone.

The appearance of effusion in the parapancreatic zone in acute pancreatitis, in combination with unclear course of the disease, is an indication for percutaneous puncture followed by examination of the aspirate to determine the aseptic or infected phase of the disease. The following cytological, bacteriological and biochemical researches allow to establish the diagnosis with accuracy to 100%, to correct medical tactics at various stages of development of acute pancreatitis, to predict and prevent development of various complications.

In edematous acute pancreatitis, percutaneous interventions are used only for diagnostic purposes (obtaining an aspirate for laboratory tests), as well as to combat severe pain (chemical denervation by alcoholization of the solar plexus).

Puncture techniques for limited complications of acute pancreatitis are used:

1. As a method of radical treatment of delimited retroperitoneal inflows, phlegmon, abscesses and cysts.
2. As a stage of preparation for the next radical surgical treatment.

One of the most serious and formidable complications of acute pancreatitis is the formation of false cysts of pancreatogenic origin. If surgical tactics in the case of formed pancreatic cysts are quite clearly defined today, in the case of unformed pseudocysts the possibility and necessity of their surgical treatment have been actively discussed recently. If until recently the indications for the use of diabetic technology were traditionally considered suppuration, compression, pain and biliary syndromes, a rapid increase in the size of the cyst, recently a growing number of pancreatologists are inclined to believe that the question of timing of surgery to diagnose acute pancreatitis decided in favor of its puncture and drainage, even in the uncomplicated course of the cyst. It is during the formation of the cyst capsule (3-6 months) most often the development of life-threatening complications (suppuration, bleeding).

Pseudocysts of small volume (50-350 ml) and diameter (6-7 cm) can be cured by aspiration-puncture method, regardless of the nature of the pathological process (infected or aseptic). Typically, a small volume of pseudocyst indicates no connection to the pancreatic duct (Fig. 10).

Drainage of cysts at an earlier date can prevent potentially life-threatening complications (rupture of the pseudocyst with the appearance of its contents in the abdominal cavity, bleeding into the cyst cavity, suppuration of the cyst).

Transcutaneous treatment interventions and established pseudocysts may be effective if they have no connection to the ductal system of the gland.

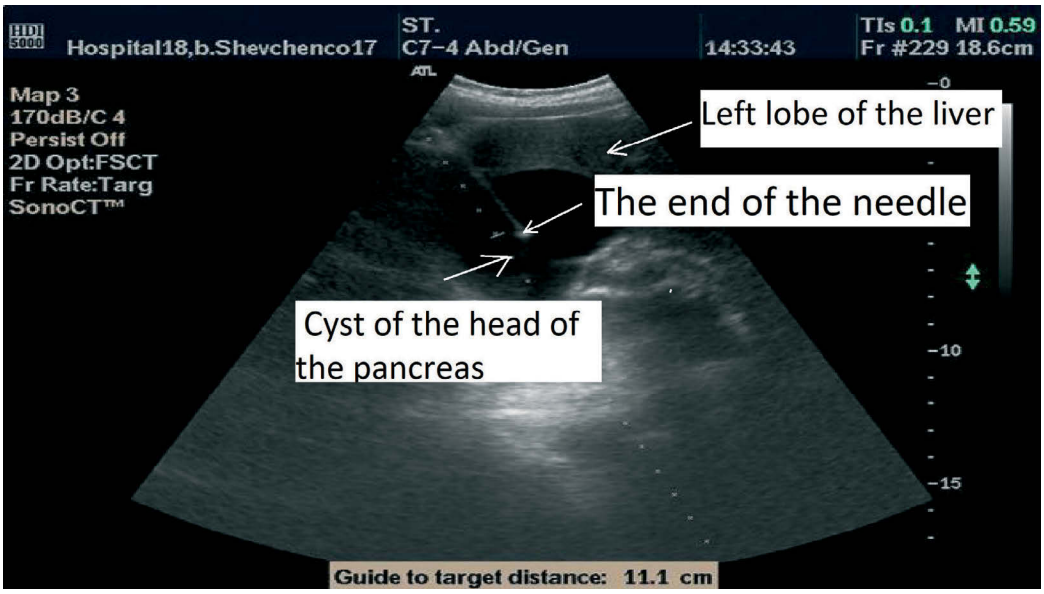

Fig. 10. Puncture of the cyst of the head of the pancreas

Purulent complications of necrotic pancreatitis remain the leading cause of death in this disease. As the echosemiotics of pancreatic necrosis and its complications have been studied in depth, the first reports of the possibility of ultrasound-guided puncture interventions in limited purulent postnecrotic formations have emerged.

Percutaneous interventions are relatively safe, highly effective in the diagnosis and treatment of patients with extensive purulent-inflammatory processes of the pancreas, allow to obtain good results in the treatment of patients at increased surgical risk, and in some cases avoid surgical treatment or relaparotomies.

Quite often phlegmons of retroperitoneal tissue, by the end of the 2nd week of their development, cause the formation of small or large intestinal fistulas. Prior to the introduction into clinical practice of minimally invasive techniques that allow X-ray examination of foci of destruction of retroperitoneal tissue, intestinal fistulas were considered rare complications of destructive pancreatitis. The use of percutaneous interventions for large retroperitoneal phlegmons is the primary surgical manipulation, which allows, first of all, to clarify the diagnosis (bacteriological studies and correction of antibacterial therapy, contrast studies to determine the length of foci of destruction and their possible connection with the abdominal cavity). Opportunities to stabilize the patient's condition (puncture and drainage of foci available for interventions) with subsequent surgical treatment in a more favorable period.

Analysis of research shows that, despite the high level of development of modern purulent surgery, the development of new methods of surgery, a powerful arsenal of highly effective antibacterial drugs, improving the basic principles of antiseptics and preventive measures, the treatment and prevention of limited purulent foci of the abdominal cavity. resolved [10, 11]. However, in a significant percentage of cases, traditional surgical interventions for abscesses may be limited to the rehabilitation and external drainage of the abscess, which is almost indistinguishable from the ultimate goal of percutaneous interventions. Performing medical punctures involves maximum removal of the abscess, repeated remediation of cavities with solutions of antiseptics and the introduction of broad-spectrum antibiotics (until receiving an antibioticogram), and then, as with drainage, etiotropic antibacterial therapy. In some cases (in the presence of thick manure or small sequesters) transdrainage administration of proteolytic enzymes is used.

The choice of drainage method, two-time according to the method of Seldinger, or one-time according to the method of a stiletto catheter, depends on the location and size of the purulent focus. It is possible to correct the number and location of drainages during treatment, which is an important feature of this method of treatment.

Control over the dynamics of the hearth is carried out using ultrasound, less often - by performing abscessography or computed tomography (Fig. 11). If necessary, Seldinger drainages can be replaced with drainages of larger or smaller diameter, their location can be corrected during treatment.

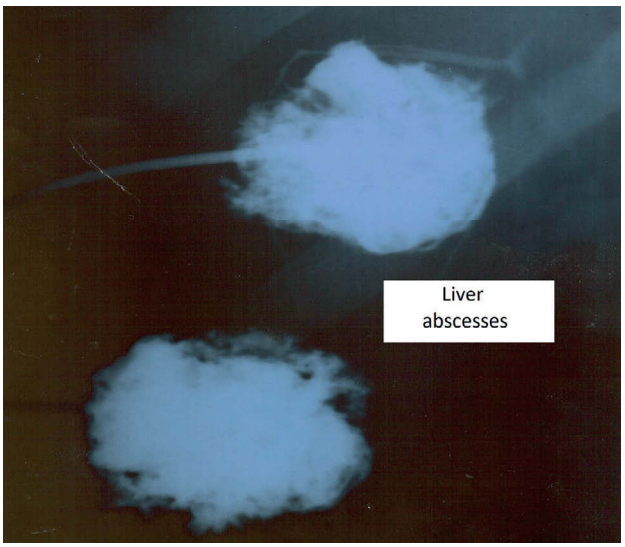

Fig. 11. Abscesses of the right lobe of the liver. Puncture and drainage of abscesses. Abscessography

Criteria for the effectiveness of this method of treatment is the stabilization of the general condition of the patient, a sharp decrease or disappearance of secretions or the most pathological formation in the control study.

Criteria for treatment and cessation of treatment are as follows:

1. Reduction of the residual cavity to 1/3 of the original.
2. A small amount of discharge from the cavity or its complete absence.
3. Change in the nature of secretions (from purulent to serous).
4. Stabilization of the general condition of the patient.
5. Steady tendency to normalization of laboratory parameters.
6. Negative results of control bacteriological research.
7. Disappearance or reduction in the volume of reactive effusion in the abdominal or pleural cavities.

At the sizes of abscesses to 4-5 centimeters preference is given to puncture treatment. The size of the abscesses is more than 5 centimeters, the presence of several foci or the ineffectiveness of puncture treatment are indications for percutaneous drainage or a combination of techniques.

In the treatment of long-term abscesses with a thickened capsule, thick contents, the presence of sequesters, as well as the presence of several connecting cavities, trans-drainage administration of protein enzymes is effective, which can reduce drainage time by 4-5 gains.

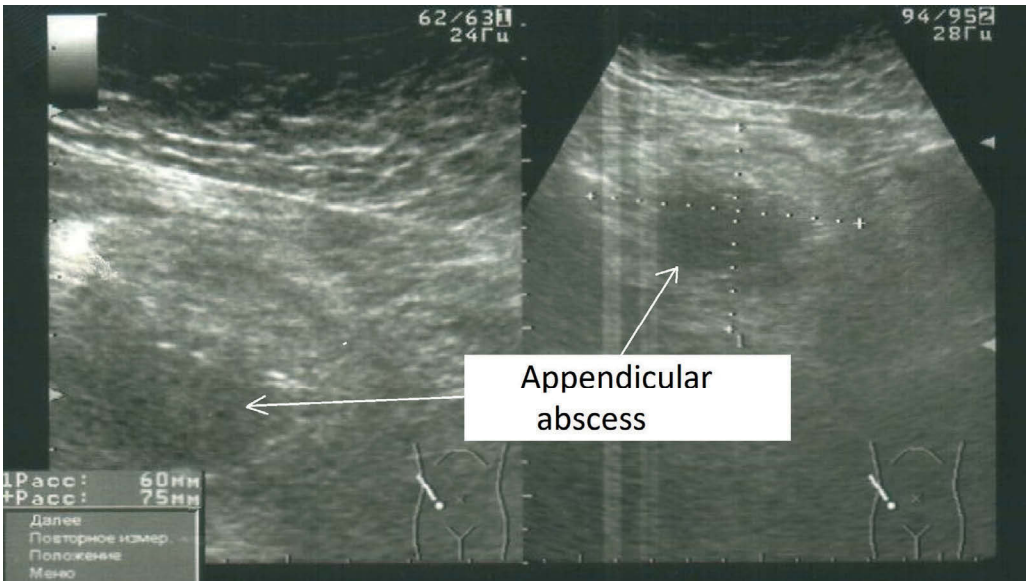

Fig. 12. Appendicular abscess. Puncture of the abscess

Due to skin intervention, they have also been shown to be effective in the treatment of post-traumatic, primarily unorganized or privately organized hematomas of the liver, post-traumatic white and bone livers, which are bent.

At extraorganic localization of the limited purulent pathology (abscess) the choice of a technique is defined by an arrangement of the purulent center concerning abdominal organs, ie degree of its availability and the sizes.

The subphrenic location of the abscess is an indication for drainage by one of the methods, most often a stylet catheter with the preferred installation of two catheters or double lumen drainage for permanent irrigation of the pathological cavity. Terms of drainage at this pathology fluctuate from 7 to 21 days.

At a subhepatic arrangement or interloop localization of abscesses medical punctures are used because most often these abscesses of the small sizes with limited availability to them (loops of intestines). The number of interventions varies in the amount of 1-3 - in the subhepatic location, and 3-6 - in inter-loop abscesses (Fig. 12).

Thus, percutaneous interventions are highly effective minimally invasive methods of surgical treatment of various postoperative formations of purulent-inflammatory origin (bile inflows, unorganized hematomas, abscesses), and which in 51.4-65% of cases may become the final method of their treatment. Percutaneous echo-controlled invasions are used to eliminate unlimited intra-abdominal and retroperitoneal fluid accumulations (ascites, reactive pleurisy), primarily with small amounts of fluid, which makes it difficult and dangerous to use traditional techniques. These interventions are an effective method of treating early postoperative complications in abdominal surgery, which requires widespread clinical use in surgical hospitals in the country.

Punctures and drainage under the control of sonography should be considered the method of choice in the treatment of a number of surgical diseases of the abdominal cavity, retroperitoneal space.

The total positive effect in the form of complete healing of abscesses and other fluid postoperative formations of the abdominal cavity and its organs by percutaneous interventions under the control of ultrasound is about 85-97%.

Comparative safety, speed of execution, informativeness and efficiency, high economic efficiency - determining factors for wide clinical introduction in domestic medicine of a method of percutaneous interventions under the control of ultrasound. However, it should be noted that the implementation of these interventions under the control of ultrasound requires strict adherence to the indications, the technique of execution. They must be performed by highly qualified specialists with knowledge of the basics of radiation diagnostics, surgery, topographic and ultrasound anatomy in a specialized surgical hospital equipped with modern equipment and tools.

Clinic of the Department of Surgery №1 Bogomolets National Medical University has experience in the successful treatment of more than 1,000 patients with diseases of the abdominal cavity, in which puncture methods of surgical treatment were used.

CONCLUSIONS

1. Percutaneous-transhepatic interventions under ultrasound control are one of the most effective methods of biliary decompression in MJ (Mechanical Jaundice)

of tumor and benign origin, in the treatment of intra-abdominal abscesses and other fluid accumulations of the abdominal cavity, retroperitoneal space, etc.

2. Diagnostic punctures under the control of ultrasound - a method of differential diagnosis of limited pathology of the abdominal cavity and its organs, which increases the efficiency of detection of purulent pathology to 100%.

3. Bacteriological examination of the obtained aspirate allows to determine the microflora, sensitivity to antibacterial drugs and to conduct etiotropic therapy.

4. Clear definition of access for percutaneous interventions under the control of ultrasound, compliance with all techniques, complete rehabilitation of the biliary tract or purulent foci in combination with comprehensive conservative treatment of patients - the main components of achieving a positive result.

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ДОСВІД ВИКОНАННЯ ПУНКЦІЙНИХ ТА ДРЕНУЮЧИХ ХІРУРГІЧНИХ МІНІІНВАЗИВНИХ ВТРУЧАНЬ ПІД УЛЬТРАЗВУКОВИМ КОНТРОЛЕМ У ДІАГНОСТИЦІ ТА ЛІКУВАННІ ЗАХВОРЮВАНЬ ОРГАНІВ ЧЕРЕВНОЇ ПОРОЖНИНИ ТА ПІСЛЯОПЕРАЦІЙНИХ УСКЛАДНЕНЬ. Огляд

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Резюме. У статті представлено описання основних пункційних та дренуючих втручань з указанням методики їх виконання, техніки, матеріалів, які використовуються для їх виконання. Описано власний досвід застосування вказаних мініінвазивних втручань у лікуванні синдрому механічної жовтяниці доброякісного та злоякісного генезу, гострого холециститу, гострого панкреатиту та його ускладнень, печінкових абсцесів, обмежених рідинних скупчень черевної порожнини та заочеревинного простору. Відмічено переваги та недоліки, проведена порівняльна оцінка та надані рекомендації щодо застосування різних пункційно-дренуючих втручань залежно від виду патології, при яких вони використовуються.

Ключові слова: механічна жовтяниця, ендобіліарні втручання, черезшкірно-черезпечінкова холангіостомія, черезшкірно-черезпечінкова холецистостомія, післяопераційні рідинні скупчення.

ОПЫТ ВЫПОЛНЕНИЯ ПУНКЦИОННЫХ И ДРЕНИРУЮЩИХ ХИРУРГИЧЕСКИХ МАЛОИНВАЗИВНЫХ ВМЕШАТЕЛЬСТВ ПОД УЛЬТРАЗВУКОВЫМ КОНТРОЛЕМ В ДИАГНОСТИКЕ И ЛЕЧЕНИИ ЗАБОЛЕВАНИЙ ОРГАНОВ БРЮШНОЙ ПОЛОСТИ И ПОСЛЕОПЕРАЦИОННЫХ ОСЛОЖНЕНИЙ. Обзор

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Резюме. В статье представлены описание основных пункционных и дренирующих вмешательств с указанием методики их выполнения, техники, материалов, используемых для их выполнения. Описан собственный опыт применения указанных миниинвазивных вмешательств в лечении синдрома механической желтухи доброкачественного и злокачественного генеза, острого холецистита, острого панкреатита и его осложнений, печеночных абсцессов, ограниченных жидкостных скоплений брюшной полости и забрюшинного пространства. Отмечены преимущества и недостатки, проведена сравнительная оценка и даны рекомендации по применению различных пункционно-дренирующих вмешательств в зависимости от вида патологии, при которых они используются.

Ключевые слова: механическая желтуха, ендобилиарные вмешательства, чрескожно-черезпеченочная холангиостомия, чрескожно-черезпеченочная холецистостомия, послеоперационные жидкостные скопления.

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POSSIBILITIES OF REGENERATION OF THE MUSCLES OF THE SOFT PALATE DURING ITS NONUNION DEPENDING ON THE MYOGENIC POTENTIAL OF STEM CELLS. Review

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Relevance. Today there are more than 150 methods for eliminating congenital defects of the hard and soft palate. However, these techniques do not always lead to high functional results, which leads to repeated surgical interventions and long-term speech therapy rehabilitation. Therefore, there is a problem of prognosis of such treatment. The search for a marker for assessing the prognosis of surgical intervention is relevant. One of these markers may be the state of the myogenic potential of stem cells.

Objective: to analyze the possibility of preliminary assessment of muscle regeneration, depending on the myogenic potential of stem cells, in order to increase the effectiveness of treatment of children with non-union of the soft palate.

Method. An analytical review of the literature on keywords from the scientometric databases PubMed, Scopus, Web of Science.

Results. Satellite cells represent an adequate system model for studying the biology of adult stem cells. Satellite cells can be considered candidates for cell therapy in muscle regeneration. First, they are one of the most abundant and most accessible cells in our body. Secondly, there is a panel of specific markers that can be used to isolate satellite cells. Third, satellite cells are localized within clear boundaries of the anatomical niche, and signaling mechanisms are currently being studied. Fourth, there is the possibility of recreating muscle injuries in which satellite cells can be studied. Future research aimed at increasing the purification of satellite cells so as to maintain their low differentiation, increase the engraftment potential, as well as new approaches aimed at obtaining satellite cells from iPS cells, will help accelerate the progress and development of drugs for cell therapy in the treatment of muscle degenerative diseases.

Conclusions. The data on the myogenic potential of stem cells, in muscle regeneration, obtained on satellite cell models, can be used to increase the effectiveness of the treatment of children with nonunion of the soft palate.

Key words: nonunion of the upper lip and palate, muscle injury, satellite stem cells, engraftment, myofibrils, marker

Relevance. Nonunion of the upper lip and palate is the most common congenital malformation of the maxillofacial region. There is a tendency to an increase in the birth rate of children with this pathology. The incidence of lip and palate unions is approximately 1: 500-1: 1000 live births.

The anatomy of deformation disorders of the maxillofacial region with non-union of the upper lip and palate reflects not only the different length and size of the defect that arose during embryonic development, but also the long-term consequences of a violation of the growth model of development in the absence of intact labial muscles and structural support by the bone arch, the presence of a message between the mouth and nose [9].

There are more than 150 methods for eliminating congenital defects of the hard and soft palate. Surgical treatment of congenital nonunions of the palate is carried out by moving the mucoperiosteal flaps. Over the years, the authors have proposed using various surgical techniques to optimize the ratio of the length of the soft palate and the width of the mesopharygus.

However, these techniques do not always lead to high functional results, which leads to repeated surgical interventions and long-term speech therapy rehabilitation.

There is a problem of choosing the most adequate technique for each specific case. Therefore, the actual issue is the search for a marker when choosing a technique. One of these markers may be the state of the myogenic potential of stem cells.

Objective: to analyze the possibility of preliminary assessment of muscle regeneration, depending on the myogenic potential of stem cells, in order to increase the effectiveness of treatment of children with non-union of the soft palate.

METHOD

To analyze the possibility of preliminary assessment of muscle regeneration, depending on the myogenic potential of stem cells, in order to increase the effectiveness of treatment of children with non-union of the soft palate.

RESULTS AND DISCUSSION

The effectiveness of primary uranostaphyloplasty is diverse. Thus, cicatricial of the tissues of the soft palate and its shortening were observed in 19-68% of patients operated on according to known methods. The main indicator of the functional efficiency of the performed uranostaphyloplasty is good pharyngeal closure. It is it that largely determines the «purity» of speech [23].

The muscles of the soft palate (5 pairs) form an aponeurosis in the center of the soft palate. The lack of connection to the skeleton at one end contributes to the development of static contractions and high tension. The main function of the soft palate in humans is to control

the flow of air through the mouth or nasopharynx during a conversation and to protect against the ingress of food and liquid into the nasal cavity during swallowing. It also plays an important role in middle ear breathing and ventilation. For the normal functioning of the palatopharyngeal ring, the muscles of the soft palate contract as synergists, and if they do not join, this is not, since they have a pathological attachment, namely: the muscles are attached to the posterior surface of the hard palate. Accordingly, the muscles do not work, and we can talk about dystrophy of muscle fibers and a decrease in myogenic potential. Surgical treatment aimed at eliminating anatomical and functional defect, which should subsequently improve speech quality and feeding. However, problems often persist after surgery. After surgery, scar tissue is formed, which subsequently causes problems with the function of the muscles of the soft palate, namely: it disrupts the organization and construction of new muscle fibers, and the connections between them [8].

By histochemical reaction to myofibrillar ATPase (mATPase), two main types of muscle fibers are distinguished - type I and II. Type II fibers are classified into type IIA, IIAB, IIB and IIC depending on the dye density after acidic preincubation. The additional type of IM fibers is usually present in the muscles that close the jaw of a person. mATPase is located on the myosin heavy chain (MyHC), a molecule that is the main contractile protein in muscles [22]. The main MUNS isoforms that are expressed in human limb muscles are slow MyHC, fast A MyHC and fast X MyHC. Slow MyHC is present in type I fibers and co-expressed with fast MyHC in type IIC fibers. Fast A MyHC is mainly present in type IIA fibers, and fast X MyHC, but not B MyHC, in type IID fibers. Additional MyHC isoforms such as fetal, embryonic, α-cardiac, and slow tonic are usually not expressed in muscle fibers of adult limbs, but are present in cranial muscles and intrafusal fibers of muscle spindles [23].

It has been established that each muscle of the soft palate has characteristic differences and that they are more similar to the muscles of the face than the limbs. The palatopharyngeal (palatopharingeus) and lingular (uvula) muscles contain the highest proportion of type II fibers among human muscles (only the facial m. Zygomaticus minor is comparable), which are characterized by fast contractility with a large high threshold of motor units. In contrast, the levator and tensor veli palatini muscles contain predominantly type I fibers.

Fetal-myosin MyHC is present in a small number of fibers in all muscles of the palate. In the limbs, fetal-myosin is only expressed during early fetal muscle development. The muscles of the palate are characterized by the presence of small fibers of less polygonal shape and a higher content of connective tissue. The same morphology is characteristic of the human facial muscles. Their fiber diameter is smaller and exhibits significant variability. All muscles have a high capillary density and an unusually high activity of mitochondrial enzymes in type II fibers. This indicates a high potential for aerobic metabolism and therefore resistance to fatigue. The absence of conventional muscle spindles indicates a special system of proprioceptive control, which is usually mediated by muscle spindle receptors. The absence of muscle spindles is important for regulating the tension and rate of contraction in the limb muscles. In the masticatory muscles, numerous muscle fibers are observed, while in the facial muscles they are completely absent [19].

A number of pathological conditions, including congenital myopathies, dystrophies, are associated with progressive loss of muscle mass and strength, and may also be accompanied by a decrease in the number and proliferative potential of satellite cell muscles. The main mechanisms responsible for these changes in the affected muscles have not yet been elucidated, but may be associated with internal changes, namely: the inclusion of proliferative stress associated with the need for repeated muscle regeneration in response to chronic degenerative conditions. However, in addition to internal deficits, environmental changes can occur that can affect the pools and suppress the myogenic activity of these cells.

Children with various types of congenital defects, which include congenital nonunion of the palate, in which the functional state of the muscles is of paramount importance, are also a problem. However, at the moment there is no idea about the primary state of the muscles of the soft palate in such patients. Therefore, the reasons for the unsatisfactory results of surgical treatment can be both congenital myopathy of the muscles of the soft palate or a decrease in the myogenic potential before surgery, due to atrophy caused by pathological attachment, and improper functioning of these muscles.

Regeneration of skeletal muscles is of great clinical importance in muscular dystrophies and various injuries; it depends on the cambial reserve formed by myosatellite cells [4].

Satellite cells – mononuclear myogenic stem cells located between the basal lamina and the cell membrane (sarcolemma) of skeletal muscle fiber, are the main participants in postnatal muscle growth. Satellite cells were first described in 1961 by Mauro A. This discovery made it possible to solve a long-term problem: why is the number of nuclei and the size of myofibrils growing without visible nuclear divisions? As a result of subsequent electron microscopic studies, resting cells lying on the surface of the muscle fiber under its basement membrane were called satellite. They make up 2-5% of the subluminal nuclei and are mitotically inert under normal conditions, but they are activated to proliferate during postnatal growth and muscle regeneration in response to injury or exercise and begin to divide, passing through self-renewal and differentiation into a mature muscle cell. With age, the ability of skeletal muscles to regenerate decreases [18].

Typically, stem (progenitor) cells are characterized by molecular markers typical for each stage of their development. Satellite cells resting in normal adult muscle can be activated, divide, forming myoblasts, which then undergo the stages of proliferation, committing (preparation) for differentiation, and fusion into immature myocytes, which form myofibrils after maturation [14]. The activation of satellite cells is accompanied by a transition to the expression of the marker MyoD, and the expression of myogenin corresponds to commitment to differentiation. As the transcription factor Pax7 decreases and the myo-specific transcription factors MyoD and myogenin grow, myoblasts enter the phase of differentiation [14]. The manifestation of cells expressing Pax7, but not MyoD, indicates a self-renewing population of satellite cells [5]. Expression of MLC3F-tg is typical of many structural muscle genes, such as skeletal muscle actin and MyHC myosin, which characterize sarcomeres in the late stages of differentiation.

Since satellite cells move from their immediate position under the basal lamina during muscle regeneration, this formally contradicts their status as stem cells. Direct evidence of the functioning of satellite cells as myogenic progenitors was first obtained using labeled thymidine in growing or regenerating muscles and then on isolated myofibrils, which led to the general acceptance of the ability of satellite cells to give rise to myoblasts differentiating into multinucleated myofibrils [15].

One of the most important characteristics of stem cells is the ability to self-renew in vivo – long-term proliferation without concomitant differentiation. Therefore, in order to reasonably define one of the subpopulations of myosatellitocytes as myogenic stem cells, most researchers are trying to establish their ability to multiple division [3].

Self-renewal of satellite cells can occur during the initial asymmetric division of the satellite cell and/or upon the return to a dormant state of the myoblasts formed by these cells.

A small number of muscle nuclei can also be formed at the expense of non-satellite cells (interstitial or circulatory), but the possibility of them creating proliferating myogenic progenitors has not yet been established.

The recent transplantation of such single myofibrils into muscle was a good confirmation of the fact that satellite cells are indeed myogenic stem cells that form new myofibrils, as well as new satellite cells [17].

Until recently, satellite cells were considered as unipotent myogenic precursors, because their myogenic potential was manifested on isolated myofibrils. However, it turned out that satellite cells can leave the myogenic pathway (exhibit plasticity) when treated, for example, with adipogenic factors. In addition, the expression of osteogenic and adipogenic markers was found in the culture of satellite cells from a single myofibril [6].

When satellite cells isolated from mouse myofibrils were cultured, both myogenic and non-myogenic clones were obtained in blood serum, and only myogenic clones expressed myogenic transcription factors with further myofibril formation. A model of mesenchymal plasticity of skeletal muscle satellite cells is proposed. According to this model, satellite cells located in the corresponding myogenic environment enter myogenic differentiation, forming myoblasts, which turn into myofibrils. Another subpopulation of satellite cells undergoing de-homing, i.e. losing the myogenic environment, they follow a different path – mesenchymal alternative differentiation (MAD), giving non-myogenic cells like adipocytes and osteoblasts [21]. Thus, the multipotency of satellite cells is fully proven.

Adult muscle tissue can repair itself in response to direct injury, neurological dysfunction, and genetic defects. The regeneration process begins with the activation of satellite cells. Once activated, satellite cells divide, differentiate into specific types of muscle tissue, and ultimately fuse with the tissue being repaired [1].

Skeletal muscle can be damaged by injury, illness, and certain types of exercise. The lesions go through the following phases: necrosis/degeneration, inflammation, repair and scarring (fibrosis). Necrosis/degeneration is accompanied by the destruction of the plasma and basement membranes, the entry of extracellular calcium and the subsequent destruction of the myofibril. First, the surface is filled with inflammatory cells (monocytes, macrophages and T-lymphocytes. Subsequent secretion of growth factors and cytokines causes blood flow to the site of injury and intensifies the inflammatory response. Muscle regeneration begins after phagocytes clear it of necrotic tissue, therefore blocking inflammatory cells (for example, non-steroidal anti-inflammatory drugs) slows down the regeneration process, since factors secreted by macrophages may play a role in the proliferation and differentiation of myoblasts. Active muscle regeneration usually lasts 2-3 weeks after injury.

It is known that stem cells do not exist in the body by themselves, they are located in a microenvironment, which is usually denoted by the term «niche». At present, this term is usually understood as a combination of factors that ensure the viability and self-reproduction of stem cells, and the differentiation of transient daughter cells. For satellite cells, these factors include the presence of the basement membrane, extracellular matrix molecules, and the presence of neighboring cells that produce growth factors and various regulatory molecules.

Niches are part of the structural and functional units that make up tissues, and stem cells are firmly anchored in the niche with the help of adhesion molecules, for this purpose, in particular, a class of adhesion molecules called integrins is used.

An important component of the satellite cell stem niche is the basal lamina, which consists of matrix proteins – laminin, collagen and proteoglycans, interacting with

membrane proteins of the satellite cell, and is a reservoir for some growth factors. In addition, the activity of satellite cells is influenced by other types of cells from the local environment (for example, fibroblasts secreting paracrine factors, nerves acting through the myofibril, endothelial cells secreting growth factors, immune cells that promote muscle regeneration through phagocytic activity and cytokine secretion).

This anatomical position of the satellite cell niche determines the combination of signals from the myofibril, blood circulation, and extracellular matrix, which control dormancy, activation, and proliferation of the satellite cell.

Various strategies have now been tried in order to optimize and improve muscle regeneration. Injections of growth factors and transplantation of satellite cells (myosatellites) have been used with different results [8]. These approaches can be combined to optimize the treatment of muscle injuries. However, treatment still faces challenges.

Satellite cells must be isolated from cultured prior to transplantation, resulting in a loss of myogenic potential. In addition, satellite cells have low survival rates and limited migration after transplantation [16].

A number of studies and clinical trials have tested the efficacy of cell therapy for muscle regeneration and have met with rather disappointing results, namely low engraftment rates and minor improvements in muscle function [11].

Improved clinical outcomes can be achieved by using more primitive satellite cells freshly isolated from donor tissue. Nevertheless, this approach introduces its limitations due to the scarcity of satellite cells in normal skeletal muscles, relatively laborious currently methods of access to extract them from tissues, and the impossibility of increasing these cells in vivo without a strong decrease in their ability to self-renewal [7].

Thus, the effective use of the regenerative potential of satellite cells during transplantation still requires the development of new strategies that support the increase in the number of these cells while maintaining their functional engraftment potential. These factors prevent the use of stem cell therapy for muscular dystrophy.

The age characteristics of satellite cells and their regeneration capabilities should also be noted.

Several studies have shown that the decrease in muscle regeneration, the number of satellite cells and the decrease in function is directly related to age [2]. In newborn mice, satellite cell nuclei make up about 30% of myofibrils, but their number decreases with maturity, and only about 5% of the nuclei in satellite cells in the muscles of adult mice [19].

The number of cells associated with muscle fibers decreases with age [10], accompanied by a relative increase in the frequency of muscle resident FAP cells, which usually form adipose and scar tissue, as well as the time of myogenesis [20].

It was shown that the regeneration of muscle fibrils ceases to be dependent on Pax7 progenitor cells after 21 days of postnatal development. It is at this period of development that the formation of the structure of the muscle fiber is completed, the nuclei are distributed and the resting myosatellite cells are isolated. It was found that the Pax7 protein functionally not only coordinates the survival and proliferation of myosatellite cells, but also prevents their differentiation and fusion into muscle fiber, preserving the potential for regeneration in myosatellite cells. The critical period of dependence on Pax7 was also determined during the transition from myosatellitocytes to the state of stem cells, which provide skeletal muscles with the ability to regenerate. This period in mice ends on day 21 after birth. The integral role of Pax3 and Pax7 for embryonic muscle progenitors is shown, and the role of only one Pax7 for perinatal. It has also been shown that adult satellite cells do not require either Pax3 or Pax7 for muscle regeneration. This finding contradicts the generally accepted concept that «regeneration repeats development.» Changes in the genetic program of muscle stem cells during the transition from the embryonic stage to the juvenile stage and further to the adult stage prompts caution in applying the knowledge gained from embryonic research to the biology of adult stem cells. Age-dependent changes in the properties of stem cells suggest the need for a thorough analysis of the age of the cell material used in transplantation in regenerative medicine [12].

A strategy for obtaining a rapidly dividing population of human skeletal myogenic progenitor cells derived from induced pluripotent stem (iPS) cells is described. iPS cells have all the potential of embryonic stem (ES) cells, but are produced by reprogramming skin cells (fibroblasts). They can be patient-specific, which reduces the likelihood of immune rejection, and does not heighten the ethical concerns surrounding the killing of human embryos. To achieve these results, the scientists genetically modified two well-studied human iPS cell lines and a human embryonic stem cell line with the PAX7 gene. This allowed them to regulate the levels of the Pax7 protein, which is necessary for the regeneration of skeletal muscle tissue after injury. The researchers found that this regulation stimulates the differentiation of naive ES and iPS cells into muscle-forming cells. Thus, the PAX7 gene - introduced at exactly the right time – helped shape the fate of human ES and iPS cells, pushing them to differentiate into muscle progenitor cells.

Once the researchers were able to pinpoint the optimal timing of differentiation, the cells became fully functional for the resumption of muscle growth needed to treat conditions such as muscular dystrophy. Moreover, Pax7-induced progenitor cells have been shown to be much more effective in improving muscle function than human myoblasts, which have been shown in clinical trials to persist after transplantation.

The first model for soft palate regeneration after surgical injury is presented. Studies show that the anatomy and histology of the muscles of the soft palate of rats are in many ways comparable to humans. The widespread use of rodents in biomedical research provides specific immune antibodies for staining. The combination of ease of handling and low cost makes rats the most suitable animal models. The model includes an isolated non-union of the soft palate. Pax7-, Muod- and MyoG-positive cells were found at the wound edges, the presence of activated SatCs and myofibril differentiation was demonstrated.

The results of the research carried out are relevant and important for solving the problems of modern maxillofacial surgery. This is especially true of congenital pathology of the maxillofacial region, since a congenital anomaly of development leads to deformation of the middle third of the face, disharmony in the development of the facial skeleton, grossly disrupts the functions of various vital organs and systems, of the facial aesthetics and negatively affects the formation of the psycho-emotional status of the child.

CONCLUSIONS

Satellite cells represent an adequate system model for studying the biology of adult stem cells, as well as potential candidates for cell therapy in muscle regeneration. First, they are one of the most abundant and most readily available cells in our body. Second, there is a panel of specific markers that can be used to isolate satellite cells. Third, satellite cells are localized within distinct anatomical niches, and signaling mechanisms are currently being studied. Fourth, there is the possibility of reconstructing muscle injuries in which satellite cells can be studied. Future research aimed at increasing the purification of satellite cells so as to maintain their low differentiation, increase the engraftment potential, as well as new approaches aimed at obtaining satellite cells from iPS cells, will help accelerate the progress and development of drugs for cell therapy in the treatment of muscle degenerative diseases.

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МОЖЛИВОСТІ РЕГЕНЕРАЦІЇ М'ЯЗІВ М'ЯКОГО НЕБА ПРИ ЙОГО НЕЗРОЩЕННІ ЗАЛЕЖНО ВІД МІОГЕННОГО ПОТЕНЦІАЛУ СТОВБУРОВИХ КЛІТИН. Огляд

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Резюме. Вагініт є загальною проблемою для жінок у всьому світі, з багатьма побічними ефектами. Вагініт – одна з найбільшАктуальність. Сьогодні існують більш 150 методик усунення вроджених дефектів твердого та м'якого піднебіння. Однак ці прийоми не завжди приводять до високих функціональних результатів, що призводить до повторних оперативних втручань і тривалої логопедичної реабілітації. Тому існує проблема прогнозу такого лікування. Актуальним є пошук маркера для оцінки прогнозу хірургічного втручання. Одним з таких маркерів може бути стан міогенного потенціалу стовбурових клітин.

Мета. Проаналізувати можливість попередньої оцінки (на дохірургічному етапі) регенерації м'язів, в залежності від міогенного потенціалу стовбурових клітин, з метою підвищення ефективності лікування дітей з незрощенням м'якого піднебіння.

Метод. Аналітичний огляд літератури за ключовими словами з наукометрічекіх баз PubMed, Scopus, Web of Science.

Результати. Сателітні клітини можуть розглядатися, як кандидати для клітинної терапії в м'язовій регенерації. По-перше, вони одні з найпоширеніших і найбільш доступних клітин в нашому організмі. По-друге, є панель конкретних маркерів, які можуть бути використані для виділення клітин-сателітів. По-третє, сателітні клітини локалізовані в чітких межах анатомічної ніші, і сигнальні механізми в даний час вивчені. По-четверте, є можливість відтворення м'язових травм, при яких сателітні клітини можуть бути вивчені. Майбутні дослідження, спрямовані на підвищення очищення сателітних клітин таким чином, щоб зберігалася їхнє низьке диференціювання, підвищувався потенціал приживлення, а також нові підходи, спрямовані на отримання сателітних клітин від iPS-клітин, допоможуть прискорити прогрес і розробку ліків для клітинної терапії при лікуванні м'язових дегенеративних захворювань.

Висновок. Сателітні клітини є адекватною моделлю системи для вивчення біології дорослих стовбурових клітин.

Ключові слова: незрощення верхньої губи та піднебіння, м'язова травма, сателітні стовбурові клітини, приживлення, міофібрили, маркер.

ВОЗМОЖНОСТИ РЕГЕНЕРАЦИИ МЫШЦ МЯГКОГО НЕБА ПРИ ЕГО НЕСРАЩЕНИИ В ЗАВИСИМОСТИ ОТ МИОГЕННОГО ПОТЕНЦИАЛА СТВОЛОВЫХ КЛЕТОК. Обзор

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Актуальность. Сегодня существуют более 150 методик устранения врожденных дефектов твердого и мягкого неба. Однако эти приемы не всегда приводят к высоким функциональным результатам, что приводит к повторным оперативным вмешательствам и продолжительной логопедической реабилитации. Поэтому существует проблема прогноза такого лечения. Актуальным является поиск маркера для оценки прогноза хирургического вмешательства. Одним из таких маркеров может быть состояние миогенного потенциала стволовых клеток.

Цель. Проанализировать возможность предварительной оценки (на дохирургическом этапе) регенерации мышц, в зависимости от миогенного потенциала стволовых клеток, с целью повышения эффективности лечения детей с несращением мягкого неба.

Метод. Аналитический обзор литературы по ключевым словам из наукометричеких баз PubMed, Scopus, Web of Science.

Результаты. Сателлитные клетки могут рассматриваться, как кандидаты для клеточной терапии в мышечной регенерации. Во-первых, они одни из самых распространенных и наиболее доступных клеток в нашем организме. Во-вторых, есть панель конкретных маркеров, которые могут быть использованы для выделения клеток-сателлитов. В-третьих, сателлитные клетки локализованы в четких пределах анатомической ниши, и сигнальные механизмы в настоящее время изучены. В-четвертых, есть возможность воссоздания мышечных травм, при которых сателлитные клетки могут быть изучены. Будущие исследования, направленные на повышение очистки сателлитных клеток таким образом, чтобы сохранялась их низкая дифференцировка, повышался потенциал приживления, а также новые подходы, направленные на получение сателлитных клеток от iPS-клеток, помогут ускорить прогресс и разработку лекарств для клеточной терапии при лечении мышечных дегенеративных заболеваний.

Вывод. Сателлитные клетки представляют собой адекватную модель системы для изучения биологии взрослых стволовых клеток.

Ключевые слова: несращение верхней губы и неба, мышечная травма, сателлитные стволовые клетки, приживление, миофибриллы, маркер