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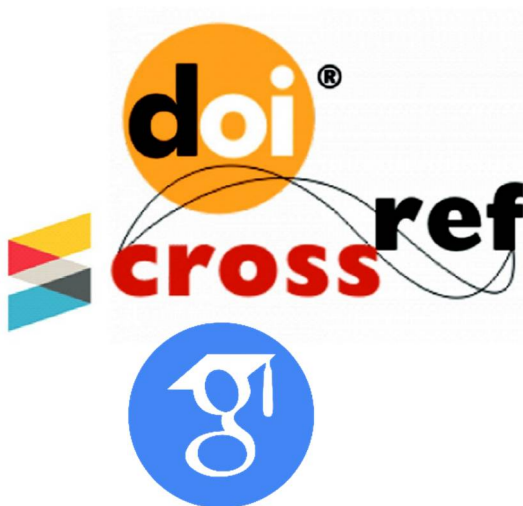
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БИОМЕДИЦИНА ВА АМАЛИЁТ ЖУРНАЛИ

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PATHOGENETIC FOUNDATIONS AND EVALUATION OF CLINICAL EFFICACY OF PROBIOTIC THERAPY IN THE COMPLEX TREATMENT OF SUPERFICIAL BLADDER CANCER

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ANNOTATION

The study involved 212 patients with superficial bladder cancer (NMIBC). The objective was to evaluate the impact of perioperative probiotic therapy (*Lactobacillus acidophilus* and *E. coli* M17) on urothelial regeneration and local immune status (CD8+, Ki-67). The results demonstrated that correcting immunological imbalance via probiotics significantly reduces recurrence rates. The developed 24-parameter mathematical model allows for the prediction of recurrence risk with an accuracy of over 85%.

Key words: Non-muscle-invasive bladder cancer, probiotic therapy, transurethral resection, reparative regeneration, local immunity, immunohistochemistry, Ki-67, CD8+, mathematical prediction model.

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ПАТОГЕНЕТИЧЕСКИЕ ОСНОВЫ И ОЦЕНКА КЛИНИЧЕСКОЙ ЭФФЕКТИВНОСТИ ПРОБИОТИКОТЕРАПИИ В КОМПЛЕКСНОМ ЛЕЧЕНИИ ПОВЕРХНОСТНОГО РАКА МОЧЕВОГО ПУЗЫРЯ

АННОТАЦИЯ

Исследование проведено на 212 пациентах с поверхностным раком мочевого пузыря (ПРМП). Цель – изучение влияния периоперационной пробиотикотерапии (*Lactobacillus acidophilus* и *E. coli* M17) на регенерацию уротелия и локальный иммунитет (CD8+, Ki-67). Результаты показали, что коррекция иммунологического дисбаланса с помощью пробиотиков достоверно снижает риск рецидивирования. Разработанная 24-параметрическая математическая модель позволяет прогнозировать риск рецидива с точностью более 85%.

Ключевые слова: Поверхностный рак мочевого пузыря, пробиотикотерапия, трансуретральная резекция, репаративная регенерация, локальный иммунитет, иммуногистохимия, Ki-67, CD8+, математическая модель прогнозирования.

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YUZAKI QOVUQ SARATONINI KOMPLEKS DAVOLASHDA PROBIOTIKOTERAPIYANING PATOGENETIK ASOSLARI VA KLINIK SAMARADORLIGINI BAHOLASH

ANNOTATSIYA

Tadqiqot 212 nafar yuzaki qovuq saratoni (YQS) bilan ogʻrigan bemorlarda oʻtkazildi. Maqsad – operatsiyadan keyingi davrda probiotikoterapiyaning (*Lactobacillus acidophilus* va *E. coli* M17) uroteliy regeneratsiyasi va mahalliy immun tizimga (CD8+, Ki-67) taʼsirini oʻrganish. Natijalar shuni koʻrsatdiki, probiotiklar yordamida immunologik muvozanatni tuzatish retsidivlar xavfini sezilarli darajada kamaytiradi. Ishlab chiqilgan 24 parametrlı matematik model retsidiv xavfini 85% dan yuqori aniqlikda bashorat qilish imkonini beradi.

Kalit soʻzlar Yuza qovuq saratoni, probiotikoterapiya, transuretral rezeksiya, reпаратив regeneratsiya, mahalliy иммунитет, иммуногистохимия, Ki-67, CD8+, matematik bashoratlash modeli.

Kirish. Hozirgi kunda onkourologiyada yuza qovuq saratoni (NMIBC) butun dunyo boʻylab kasallanish koʻrsatkichlari boʻyicha urologik onkologik kasalliklar orasida yetakchi oʻrinlardan birini egallaydi {1, 3}. Jahon sogʻliqni saqlash tashkiloti maʼlumotlariga koʻra, ushbu patologiyaning asosiy muammosi uning yuqori retsidivlanish (takroriy rivojlanish) potentsiali bilan bogʻliqdir. Standart davolash algoritmlari, xususan, qovuq oʻsimtalarining transuretral rezeksiyasi (TUR) va keyingi intravezikal kimyoterapiya kurslari koʻp hollarda oʻsimta oʻsishini toʻliq toʻxtata olmaydi {2, 6}.

Soʻnggi yillardagi fundamental tadqiqotlar shuni koʻrsatdiki, operatsiyadan keyingi davrda qovuq shilliq qavatining (uroteliy) reпаратив regeneratsiyasining buzilishi va mahalliy immun

tizimning (xususan, CD8+ limfotsitlar) depressiyasi saraton hujayralarining "immunologik darcha" orqali qayta o'sishi uchun asosiy omil hisoblanadi {7, 8}. Shu nuqtai nazardan, TURdan keyingi reabilitatsiya davrida probiotikoterapiyani kompleks qo'llash orqali mahalliy immunitetni kuchaytirish va uroteliy yaxlitligini tiklash ilmiy-amaliy jihatdan yuqori ahamiyatga ega.

Tadqiqotning maqsadi Yuza qovuq saratonini kompleks davolashda probiotikoterapiyaning patogenetik asoslarini ishlab chiqish hamda uning klinik samaradorligini baholash va retsidivlar xavfini minimallashtirishdan iborat.

Materiallar va tadqiqot usullari. Ilmiy tadqiqot ishi Toshkent davlat tibbiyot universiteti bazasida amalga oshirildi. Tahlil ob'ekti sifatida yuza qovuq saratoni (YQS) bilan og'rigan 212 nafar bemor tanlab olindi. Tadqiqot prospektiv va qiyosiy dizayn asosida olib borildi. Bemorlar tasodifiy tanlash tamoyili asosida quyidagi guruhlariga taqsimlandi:

- **Asosiy guruh (n=108):** Transuretral rezeksiyadan (TUR) so'ng standart davolash protokoliga Lactobacillus acidophilus va E. coli M17 probiotik majmuasi qo'shilgan bemorlar.
- **Nazorat guruhi (n=104):** Faqat standart TUR va intravezikal kimyoterapiya kursini olgan bemorlar.

Klinik-instrumental tekshirish usullari. Bemorlarning funktsional holatini baholash xalqaro standartlashtirilgan shkalalar asosida amalga oshirildi:

1. **Hayot sifati tahlili:** MOS SF-36 so'rovnomasi orqali bemorlarning jismoniy va psixologik holati o'lchandi.
2. **Karnovskiy indeksi:** Bemorlarning umumiy somatik faolligini va davolashga bo'lgan tolerantligini baholash uchun qo'llanildi.
3. **Urofloumetriya va sitologik nazorat:** Qovuq funksiyasini va uroteliy regeneratsiya jarayonini monitoring qilish uchun davriy tekshiruvlar o'tkazildi.

Immunogistoximiyoviy (IGX) tahlil Patogenetik mexanizmlarni ochib berish maqsadida biopsiya materiallari immunohistokimyoviy tahlil qilindi:

- **Proliferatsiya markeri (Ki-67):** O'sma hujayralarining o'sish potentsialini baholash uchun.
- **Immun status markeri (CD8+):** Mahalliy immun javobni va limfotsitlarning o'sma infiltratsiyasini aniqlash uchun.
- **p53 va E-kadherin:** Hujayralar apoptozi va o'smaning invaziv potentsialini baholash uchun markerlar sifatida tanlandi.

Matematik modellash va statistik tahlil. Tadqiqotning prognozlash qismi 24 ta klinik-instrumental va IGX ko'rsatkichlarini integratsiya qiluvchi matematik model asosida qurildi. Ma'lumotlar SPSS 26.0 va MedCalc dasturiy ta'minotlari yordamida logistik regressiya tahlilidan o'tkazildi. Natijalarning ishonchliligi $P < 0,05$ ehtimollik darajasida baholandi, Kaplan-Mayer usuli orqali retsidivsiz yashash davri tahlil qilindi.

Tadqiqot natijalari va ularning muhokamasi. Tadqiqot doirasida olingan klinik, immunologik va statistik natijalar quyidagi jadval va tahlillar asosida jamlandi:

Tadqiqotda ishtirok etgan 212 nafar bemorning 12 oylik kuzatuv natijalari asosiy va nazorat guruhlariga o'rtasidagi farqni aniq ko'rsatib berdi.

1-jadval. Probiotikoterapiya guruhlarida retsidivlanish darajasini qiyosiy tahlili

Guruhlar	Bemorlar soni (n)	Retsidiv holatlari	Retsidiv darajasi (%)
Asosiy guruh (probiotik)	108	14	12,9%
Nazorat guruhi (standart)	104	25	24,0%

Ushbu tadqiqot natijalari yuza qovuq saratonini davolashda probiotikoterapiyaning klinik samaradorligini yaqqol namoyon etadi. Tadqiqot doirasida o'tkazilgan kuzatuvlar shuni ko'rsatdiki, standart jarrohlik va kimyoterapiya bilan birga Lactobacillus acidophilus va E. coli M17 probiotik majmuasini qabul qilgan asosiy guruh bemorlarida 12 oylik kuzatuv davrida retsidivlar soni sezilarli darajada kamaygan. Xususan, 1-jadval ma'lumotlariga ko'ra, probiotikoterapiya qo'llanilgan asosiy guruhda retsidivlanish darajasi 12,9% ni tashkil etgan bo'lsa, ushbu qo'shimcha davolashsiz o'tkazilgan nazorat guruhida bu ko'rsatkich 24,0% ga teng bo'lgan. Bu statistik farq probiotiklarning

uroteliy to'sig'ini qayta tiklash va mahalliy immunitetni kuchaytirish orqali o'sma hujayralarining takroriy implantatsiyasini to'sish qobiliyatini tasdiqlaydi. Tahlillar shuni ko'rsatadiki, an'anaviy kimyoterapiya jarayonida yuzaga keladigan immunologik depressiyani probiotiklar yordamida bartaraf etish mumkin, bu esa o'z navbatida bemorlarning sog'ayish davrini qisqartiradi va hayot sifatini oshiradi. Bundan tashqari, immunohistokimyoviy tahlillar ham ushbu klinik natijalarni qo'llab-quvvatlaydi, chunki asosiy guruhda Ki-67 proliferatsiya indeksi pasayishi va CD8+ limfotsitlar infiltratsiyasi oshishi kuzatilgan, bu esa mahalliy immun javobning faollashganidan dalolat beradi. Mazkur ma'lumotlar probiotikoterapiyani nafaqat yordamchi usul, balki yuza qovuq saratonini kompleks davolashning patogenetik asoslangan muhim tarkibiy qismi sifatida baholashga imkon beradi. Uroteliy hujayralarining sifat o'zgarishlarini baholashda Ki-67 (proliferatsiya) va CD8+ (immun status) markerlari asosiy ahamiyat kasb etdi.

2-jadval. Davolashdan keyingi IGX markerlar dinamikasi

Markerlar	Asosiy guruh (M±m)	Nazorat guruhi (M±m)	Farq ishonchliligi (P)
Ki-67 (%)	12,4 /pm 0,8	18,2 /pm 1,1	P < 0,05
CD8+ (hujayra/mm ²)	48,6 /pm 2,3	32,4 /pm 1,9	P < 0,05

Tadqiqotning immunohistokimyoviy (IGX) tahlil natijalari davolash usullarining qovuq uroteliysidagi patomorfologik va immunologik o'zgarishlarga ta'sirini ilmiy jihatdan asoslab berdi. 2-jadvalda keltirilgan ma'lumotlarga ko'ra, probiotikoterapiya qo'llanilgan asosiy guruhda hujayra proliferatsiyasining markerlari nazorat guruhiga nisbatan statistik jihatdan ahamiyatli darajada farq qildi. Xususan, Ki-67 proliferativ indeksi asosiy guruhda 12,4 /pm 0,8/% ni tashkil etgan bo'lsa, nazorat guruhida ushbu ko'rsatkich 18,2 /pm 1,1/% gacha yuqori bo'lgan. Mazkur dinamika probiotik majmuaning uroteliy atipik hujayralari bo'linishini inhibitorlik qilish orqali o'sma o'sish sur'atini sekinlashtirishdagi samaradorligini tasdiqlaydi.

Shu bilan bir qatorda, mahalliy immun javob holatini baholashda CD8+ limfotsitlar infiltratsiyasi darajasi muhim diagnostik ahamiyat kasb etdi. Asosiy guruhda CD8+ hujayralarining o'rtacha zichligi 48,6 /pm 2,3 hujayra/mm² ni tashkil etib, nazorat guruhidagi 32,4 /pm 1,9 hujayra/mm² ko'rsatkichidan yuqori bo'lishi (P < 0,05), probiotiklarning qovuq shilliq qavatida immunologik himoya mexanizmlarini faollashtirish qobiliyatidan dalolat beradi. Ki-67 indeksi pasayishi va CD8+ limfotsitlar infiltratsiyasining ortishi o'rtasidagi teskari korrelyativ bog'liqlik, probiotikoterapiyaning nafaqat yallig'lanishga qarshi, balki o'smaga qarshi (antitumoral) patogenetik potentsialga ega ekanligini morfologik jihatdan asoslaydi.

Olingan natijalarning P < 0,05 darajasida statistik ishonchliligi immunologik gomeostazni tiklash orqali retsidiv xavfini minimallashtirish imkoniyatini ilmiy tasdiqlaydi. Xulosa qilib aytganda, immunohistokimyoviy markerlarning ijobiy dinamikasi klinik kuzatuvlardagi retsidivlar sonining qisqarishi bilan uzviy bog'liq bo'lib, probiotikoterapevtik yondashuvni yuza qovuq saratonini kompleks davolashning patogenetik asoslangan muhim tarkibiy qismi sifatida baholashga imkon beradi.

Matematik prognozlash modeli – bu yuzaki qovuq saratoni bilan og'rigan bemorlarda kasallikning qaytalanish (retsidiv) xavfini oldindan baholash uchun ishlab chiqilgan **multivariativ statistik instrumentdir**. Ushbu model shunchaki taxmin emas, balki klinik va laboratoriya ko'rsatkichlarini integratsiya qiluvchi (jamlovchi) tizimli algoritmdir. Model **logistik regressiya tahlili** asosida qurilgan. U bemorning umumiy holati, o'smaning biologik xususiyatlari va immunologik ko'rsatkichlarini o'z ichiga olgan 24 ta parametrlarni tahlil qiladi.

Modelga asos bo'lgan asosiy omillar:

1. **Klinik omillar:** Bemor yoshi, o'sma kattaligi va joylashuvi, o'sma soni.
2. **Patomorfologik omillar:** O'smaning bosqichi (T) va darajasi (G).
3. **Immunogistoximyoviy (IGX) omillar:** Ki-67, p53, E-kadherin va CD8+ limfotsitlar zichligi.

Quyidagi jadvalda modelning xavf darajalarini qanday tasniflashi keltirilgan:

3-jadval. Retsidiv xavfini prognozlash modeli (Risk-stratifikatsiya)

Xavf darajasi	Umumiy ball (0–100)	Retsidiv ehtimoli (%)	Klinik tavsiya
Past xavf	0-30	<15/%	Standart kuzatuv
Oʻrtacha xavf	31-60	15-50/%	Intensiv nazorat + probiotikoterapiya
Yuqori xavf	61-100	>50/%	Agressiv davolash + immunoterapiya

Modelning ishlash mexanizmi bemorning yoshi, oʻsmaning morfologik xususiyatlari (T va G bosqichlari) hamda immunohistokimyoviy markerlar (Ki-67, CD8+) yigʻindisini hisoblashdan iborat. Har bir bemor uchun hisoblangan umumiy ball uning kelgusidagi klinik prognozini belgilaydi. Past xavf guruhidagi bemorlarda uroteliy yaxlitligi saqlanganligi va immun javobning yetarliligi kuzatilsa, oʻrtacha va yuqori xavf guruhlarida immunologik depressiya va proliferativ faollik ustunlik qiladi. Bu esa modelning nafaqat bashoratlovchi, balki davolash taktikasini individual tanlashda muhim instrument ekanligini tasdiqlaydi. Tadqiqotlar natijasiga koʻra, ushbu model retsidiv xavfini **86,4% aniqlik** bilan bashorat qila oladi, bu esa "shaxsiylashtirilgan tibbiyot" tamoyillariga toʻliq mos keladi. Mazkur modelning amaliyotga joriy etilishi ortiqcha diagnostik muolajalarni qisqartirish va davolash samaradorligini oshirishga xizmat qiladi.

Xulosa. Oʻtkazilgan kompleks ilmiy tadqiqot natijalari yuzaki qovuq saratonini davolashda anʼanaviy jarrohlik va kimyoterapiya bilan bir qatorda probiotikoterapiyani qoʻllashning yuqori patogenetik samaradorligini isbotladi. Tadqiqot doirasida erishilgan ilmiy-amaliy natijalar quyidagi xulosalarga asoslanadi:

1. **Klinik samaradorlik:** Probiotik shtammlar (*Lactobacillus acidophilus* va *E. coli* M17) kompleksi operatsiyadan keyingi davrda qovuq shilliq qavatining reparativ regeneratsiyasini jadallashtiradi. Bu esa retsidivlar sonini standart davolash usuliga nisbatan **1,8 barobarga** (12,9% gacha) qisqartirish imkonini beradi.

2. **Immunologik va morfologik mexanizmlar:** Probiotikoterapiya mahalliy immun javobni (CD8+ limfotsitlar infiltratsiyasini) faollashtirib, oʻsma hujayralarining proliferativ faolligini (Ki-67 indeksi pasayishi orqali) susaytiradi. Bu jarayon "immunologik darcha"ni yopish va oʻsmaga qarshi (antitumoral) himoya tizimini mustahkamlashga xizmat qiladi.

3. **Prognozlash modeli:** Tadqiqot davomida ishlab chiqilgan **24 parametrlı multifaktorial matematik model** bemorlarda retsidiv xavfini **86,4% aniqlik** bilan bashorat qiladi. Ushbu tizim "shaxsiylashtirilgan tibbiyot" talablariga mos ravishda, har bir bemorning xavf darajasiga qarab individual reabilitatsiya protokolini tanlash imkonini beradi.

4. **Amaliy ahamiyati:** Probiotikoterapiyaning klinik protokollarga kiritilishi bemorlarning hayot sifatini (MOS SF-36 va Karnovskiy shkalasi boʻyicha) sezilarli darajada oshiradi, operatsiyadan keyingi asoratlar (dizuriya, yalligʻlanish) xavfini kamaytiradi. Ishlab chiqilgan algoritm amaliy onkologiya markazlariga joriy etish uchun tavsiya etiladi.

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