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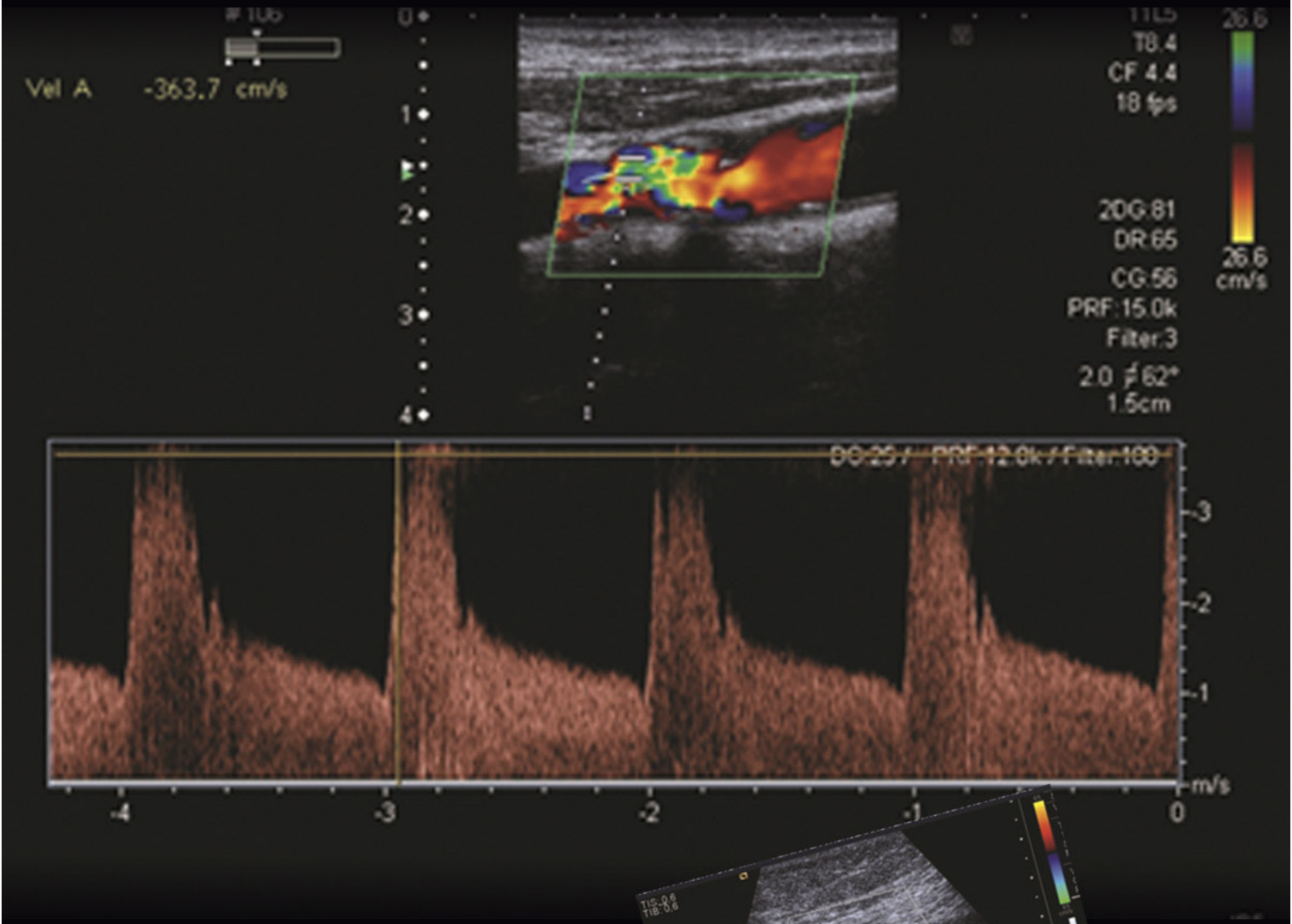

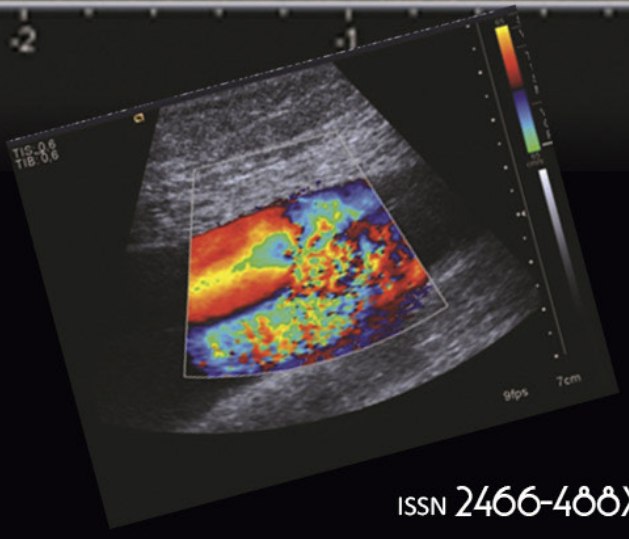

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Revijalni članak

LEČENJE HRONIČNOG KANCERSKOG BOLA KOD UROLOŠKIH BOLESNIKA

Nebojša Lađević[1,2], Vesna Jovanović[1,2], Jelena Jovičić[1], Nikola Lađević[3]

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Sažetak

Hronični kancerski bol predstavlja značajan klinički problem u celom svetu. Njegovi uzroci su multifaktorijalni i kompleksni, variraju sa nizom faktora i procesa vezanim kako za tumorski proces tako i za samog domaćina. Iako se kvalitet farmakološkog lečenja kancerskog bola popravio poslednjih decenija, smatra se da čak 1 od 3 bolesnika sa kancerskim bolom ne dobija lekove za tretman bola koji odgovaraju njegovom intenzitetu. Hronični kancerski bol kod uroloških bolesnika može da ima različite osobine, s obzirom na to da su ovi karcinomi poreklom od različitih organa (prostate, testisa, bubrega, nadbubrežne žlezde, mokraćne bešike, penisa). Karakteristično za urogenitalne neoplazme jeste da veoma često metastaziraju u kosti (kičmene pršljenove, karlicu, kosti glave) i povezane su sa patološkim frakturama, hiperkalcemijom i neurološkim deficitima, što dovodi do značajnog smanjenja kvaliteta života. Bol uzrokovan koštanim metastazama je nociceptivni bol, ali može biti i udružen sa neuropatskim bolom, ukoliko tumor izvrši kompresiju ili invaziju nerava, kičmene moždine ili nervnih pleksusa. Oko 70–90% uroloških bolesnika sa karcinomom može biti adekvatno lečeno pridržavanjem preporuka Svetske zdravstvene organizacije za tretman kancerskog bola. Međutim, često je potrebno da se u razmatranje uzme i primena dodatnih metoda, kao što su zračenje ili psihosocijalno lečenje pacijenata.

Ključne reči: *kancerski bol; terapija bola; urološke neoplazme; koštane metastaze*

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Review article

TREATMENT OF CHRONIC CANCER PAIN IN UROLOGIC PATIENTS

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Sumarry

Cancer pain remains a significant clinical problem worldwide. Cancer pain causes are multifactorial and complex and varying with a variety of factors and processes related both to the tumor process and to the host itself. Even though the quality of pharmacologic pain management has improved in the last decades, 1 in 3 patients do not receive pain medication appropriate for the intensity of experienced pain. Chronic cancer pain in urologic patients has different traits, since this carcinoma might originate from various organ:, prostate, kidneys, adrenal glands, urinary bladder or the penis. Urogenital neoplasm very often metastasized into the bones (spine, pelvis and head bones) and they are associated with pathological fractures, hypercalcemia, and neurological deficits, which lead to a significant reduction in quality of life. Pain induced by bone metastases is nociceptive pain, but may also be associated with neuropathic pain if the tumor performs compression or invasion of the nerve, spinal cord or nerve plexus. In 70–90% of urological cancer patients pain can be adequately relieved by consistent adherence to the WHO cancer pain recommendations. However, additional pain relief therapies, such as radiation and psychosocial treatment of these patients have to be considered.

Keywords: *cancer pain; pain therapy; urological neoplasm; bone metastases*

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Uvod

Hronični kancerski bol predstavlja značajan klinički problem u celom svetu. Njegovi uzroci su multifaktorijalni i kompleksni, variraju sa nizom faktora i procesa vezanim kako za tumorski proces tako i za samog domaćina. Patofiziologija hroničnog kancerskog bola i dalje nije u potpunosti razjašnjena, a najnovija laboratorijska istraživanja ukazuju na važan mehanizam unakrsne komunikacije ćelija kancera sa imunskim i neuralnim sistemom domaćina, koji može biti opšte prihvaćen za objašnjenje sindroma kancerskog bola. Iako se kvalitet farmakološkog lečenja kancerskog bola popravio poslednjih decenija, smatra se da čak 1 od 3 bolesnika sa kancerskim bolom ne dobija lekove za tretman bola koji odgovaraju njegovom intenzitetu. Takođe, ovi pacijenti su danas izloženi i novim terapijskim mogućnostima, kao što je imunoterapija, tokom relativno dugog vremenskog perioda. Neke od ovih metoda nose rizike od značajnih neželjenjih efekata, uključujući bol[1].

Termin kancerski bol nema specifičnu definiciju. To je ustvari bol koji imaju bolesnici sa karcinomom, a koji zahteva stalno praćenje[2]. Uzroci bola mogu biti različiti:

- Tumorska invazija i kompresija drugih tkiva od strane tumora
- Hirurški bol / bol posle biopsije tumora
- Bol posle radijacije (destrukcija tkiva)
- Neuropatije izazvane hemoterapijom ili nekom drugom terapijom
- Ishemija
- Inflamacija
- Visceralni bol zbog oštećenja organskih struktura ili opstrukcija
- Muskuloskeletni bol zbog smanjene pokretljivosti i artropatije
- Patološke frakture.

Kao što vidimo, jedino bol posle hirurške intervencije nastaje odmah posle samog događaja (operacije, biopsije), dok u ostalim slučajevima bol nastaje danima ili mesecima posle događaja (pojave tumora), ali je on sve jači i pogoršava se vremenom. Bol ne mora da traje konstantno, već se može javljati u intervalima, pojačavati sa pokretima ili u određenim delovima dana. Veoma je bitan i drugi aspekt bola koji zavisi od bolesnikovog doživljaja patnje. Patnja je emocionalno stanje udruženo sa biološkim i psihosocijalnim događajima koji prete integritetu individue[3].

Oko 1/3 bolesnika ima bol u trenutku dijagnoze karcinoma, dok oko 2/3 bolesnika sa uznapredovalim karcinomom bol opisuje kao umeren ili jak. Najvažnije je da 90% bolesnika sa kancerskim bolom može biti uspešno lečeno multidisciplinarnim pristupom.

Klasifikacija kancerskog bola:

1. Nociceptivni
   a. Kosti
   b. Meka tkiva
   c. Organi
2. Neuropatski
   a. Kompresija nerava
   b. Infiltracija nerava
3. Mešoviti.

Karakteristike bolnih sindroma vezanih za karcinome u urologiji su prikazani u tabeli 1. Karakteristično za ove neoplazme jeste da veoma često metastaziraju u kosti (kičmene pršljenove, karlicu, kosti glave) i povezane su sa patološkim frakturama, hiperkalcemijom i neurološkim deficitima i dovode do značajnog smanjenja kvaliteta života. Oslobađanje alogenih supstanci u tkivima, mikrofrakture i pritisak na periost su glavni uzroci bola[4]. Bol uzrokovan koštanim metastazama je nociceptivni bol, ali može biti i udružen sa neuropatskim bolom, ukoliko tumor izvrši kompresiju ili invaziju nerava, kičmene moždine ili nervnih pleksusa. Oko 1/3 bolesnika ima neuropatski bol. Nociceptivni bol se dobro lokalizuje i pojačava se pri pokretu, ali može da se javlja i u mirovanju. Neuropatski bol najčešće ima kvalitet konstantnog pečenja, žarenja i ponekad opioidi nisu dovoljni u terapiji, pa se dodaju i koanalgetici.

Svetska zdravstvena organizacija (WHO) predlaže terapiju bola po takozvanim „analgetskim stepenicama", gde se postepeno uvode sve jači analgetici. Oko 70–90% uroloških bolesnika sa karcinomom može adekvatno da se leči pridržavanjem preporuka Svetske zdravstvene organizacije za tretman kancerskog bola. Međutim, često je potrebno da se u razmatranje uzme i primena dodatnih metoda, kao što su zračenje ili psihosocijalno lečenje.

Tabela 1: Karakteristike bolnih sindroma vezanih za karcinome u urologiji

Zahvaćeno područje	Vrsta karcinoma	Najčešći opis bola	Prilog
Dugačke kosti	P	Oštar, kucajući, pritiskajući	Pojačava se sa pokretom, moguće frakture.
Pelvis	P		
Kuk	P		
Abdomen	P	Grč u abdomenu	Ukoliko je u retroperitoneumu, savijanje može smanjiti bol. Može da se širi u rame, leđa i prepone.
Abdominalna karcinomatoza	P	Kolika, tup	Praćen je dijarejom, opstipacijom, mučninom, ascitom, obstrukcijom.
Lumbalni pleksus	P	Pečenje, pritisak, kao struja	Širi se u prepone i butinu, edem parastezije, slabost.
Sakralni pleksus	P, GU	Pečenje, pritisak, kao struja	Donji deo leđa, vidi se i disfunkcija mokraćne bešike i creva, impotencija.
Kičmena moždina	P, K	Tup, u vidu obruča, steže	Bol je jači kada se leži, kašlje, nosi nešto teško.
Bolna periferna neuropatija	P	Pečenje, mravinjanje	Blagi nadražaj može biti bolan, gubitak refleksa.
Bol udružen sa uzimanjem steroida	P	Kucajući, napetost i bol	Obično prolazan bol u mišićima i zglobovima, pogoršava se sa pokretima.
Postradijaciona fibroza ekstremiteta	P	Pečenje, kao da neko vuče	Nastaje od 1 pa do 30 godina nakom radijacije, vide se i nekroze kosti, utrnulost.

P = prostata; GU = genitourinarni trakt; K = bubreg

Upotreba bisfosfonata i kalcitonina je ponekad korisna u stabilizaciji koštanog metabolizma. Epiduralna i intratekalna primena opioida može biti dovoljna za neutralisanje bola nastalog usled koštanih metastaza, a primena fenola zbog destrukcija nerava kod bolesnika sa neuropatskim bolom može da dovede do značajnog olakšanja[5,6,7].

Osnovu strategije terapije kancerskog bola predstavljaju četiri cilja nege:

1. Produženje preživljavanja
2. Optimizacija komfora
3. Optimizacija funkcionisanja
4. Odsustvo bola.

U sistemu donošenja odluka postoji i vodič kroz hijerarhiju opštih principa terapije, a koji je prikazan u tabeli 2. Vidimo da pristup svakom bolesniku mora da bude individualan i da bi se u primeni terapije trebalo voditi odnosom između rizika i koristi od određenih procedura.

Tabela 2: Hijerarhija opštih principa terapije

1	Individualna terapija za svakog bolesnika
2	Dati prednost kauzalnoj (uzročnoj) terapiji u odnosu na simptomatsku
3	Dati prednost lokalnoj terapiji u odnosu na sistemsku
4	Primeniti sistemsku terapiju prema WHO „analgetskim stepenicama”
5	Usaglasiti terapiju i sa vodičima palijativne medicine
6	Od samog početka primeniti fizikalnu terapiju i psihološko savetovanje

TERAPIJA BOLA KOD BOLESNIKA SA KARCINOMOM PROSTATE

Bol se javlja i u ranim i u kasnim stadijumima bolesti karcinoma prostate. Na početku bolesti bol je slab i bolesnik ga dobro podnosi, ali se kasnije pojačava. Bol može biti uzrokovan od strane samog kancera (77%), od strane terapije koju bolesnik prima (19%) ili ni od jednog od prethodna dva uzroka (4%). Bol se najčešće otkriva kao deo bolesti u odmaklom stadijumu, kada postoje i metastaze, pa je tada i terapija simptomatska. Sveukupna incidenca hroničnog bola kod bolesnika sa karcinomom prostate je 30–50%, ali kada bolesnici uđu u terminalnu fazu bolesti incidenca raste na 90%. Bol tada direktno zavisi od rasta i širenja tumora, pre svega u tri zone: kosti, infiltracija nerava i organa[8].

Bol zbog lokalnih promena

Bol zbog lokalnih promena nastaje zbog invazije mekih tkiva i organa. Da bi se smanjio bol, nekada je potrebno izvesti hiruršku intervenciju ili minimalno invazivne metode (plasirati urinarni kateter, stent, nefrostomija). Ukoliko zbog rasta prostate dođe do opstrukcije i nemogućnosti pražnjenja bešike, onda je neophodno napraviti suprapubičnu drenažu kateterom i osloboditi bolesnika jakog bola. Ukoliko postoji opstrukcija na nivou uretera, onda se predlaže postavljanje nefrostomije kako bi se sačuvala funkcija bubrega i otklonio bol koji nastaje kao posledica hidronefroze bubrega. Velika prostata i matastaze u limfnim čvorovima male karlice mogu da dovedu i do limfne staze sa edemima donjih ekstremiteta i razvoja bola. U cilju smanjenja bola, neohodna je primena fizikalne terapije, kako bi se poboljšala limfna drenaža i terapija osnovne bolesti. U uznapredovalom stadijumu karcinoma prostate vidi se i opstrukcija rektuma, ileus i bol koji je posledica ileusa. Ukoliko postoji mehanička opstrukcija, hirurška intervencija je neophodna, a ukoliko postoji paralitički ileus, kao posledica infiltracije nervnog pleksusa ili kao posledica primene analgetika, neophodno je poboljšati motilitet creva[8].

Bol zbog koštanih metastaza

Koštane metastaze su najčešći uzrok hroničnog bola kod bolesnika sa karcinomom prostate. Rasprostranjene koštane metastaze najčešće izazivaju multifokalni bol. Više od 25% bolesnika sa koštanim metastazama nema bol. Faktori koji prevode bezbolnu leziju u bolnu su i dalje nepoznati. Koštane metastaze mogu da izazovu bol putem aktivacije endotelnih ili periostalnih nociceptora, direktnim rastom tumora u meko tkivo ili nerve i drugim složenim mehanizmima[4].

Izbor terapije zavisi od mesta tumora, histologije, stadijuma i bolesnikovog fizičkog i emocionalnog stanja. Terapijske opcije su:

1. Hormonska terapija – koja se generalno mnogo bolje podnosi nego hemoterapija, ali ima i dosta neželjenih efekata. Nestanak bola se očekuje kod 35–70% bolesnika. Dobro diferentovani prostatični karcinom bolje reaguje na hormonsku terapiju nego slabo diferentovan. Kao hormonska terapija koriste se estrogeni, antiandrogeni, estrogen-mustin kompleks, progesteroni, aminoglutetimidi, gonadotropni RH, orhiektomija, adrenalektomija i hipofizektomija. Kortikosteroidi se takođe koriste u terapiji bola, naročito kod koštanih metastaza.
2. Radioterapija – upotreba radioterapije kod karcinoma prostate sa metastazama je značajna mera koja smanjuje bol izazvan koštanim metastazama i unapređuje kvalitet života. Kod 80% bolesnika tretiranih radioterapijom očekuje se značajno smanjenje i nestanak bola. Tehnike primene radioterapije su različite i idu od primene velike doze u jednom tretmanu, pa sve do više manjih tretmana tokom 4 nedelje. Palijativne doze su manje nego maksimalne doze[9].
3. Ortopedska hirurgija – u dugačkim kostima dolazi do smanjenja korteksa kosti kod više od 50% bolesnika sa metastazama. Najčešće je potrebno izvesti profilaktičku fiksaciju kosti, kako ne bi došlo do patoloških fraktura, a zatim postoperativno primeniti i radioterapiju. Pokazano je da su palijativne doze radioterapije povezane sa rekalcifikacijom. Ove hirurške intervencije usmerene su na ublažavanje bola, kao i na poboljšanje i očuvanje funkcionisanja i nezavisnosti pacijenta[10].
4. Radioizotopi – široko rasprostranjene koštane metastaze kod karcinoma prostate se uspešno tretiraju sa sistemski primenjenim radioizotopima. Najčešće korišćeni radionukleidi su Stroncijum-89-hlorid, Samarium-153-etilendijamintetrametilen, Fosforična kiselina,[186] Renijum-hidroksietiliden-difosfonat i Radijum-223.

Primena ove terapije smanjuje progresiju bolesti, smanjuje broj bolnih mesta, smanjuje potrebu za primenom radioterapije, smanjuje potrebu za analgeticima i poboljšava kvalitet života. Postoje primeri da radioizotopi mogu izazvati kompletni nestanak bola u periodu od 1 do 6 meseci[11].

5. Bisfosfonati – predstavljaju standardni deo terapije bolesnika sa koštanim metastazama i utiču na smanjenje bola. Oni inhibišu osteoklastnu aktivnost i posebno se koriste u tretmanu ponovnog koštanog bola i prevencije koštanih fraktura. Zoledronična kiselina, treća generacija bisfosfonata, izuzetno je efikasna u tretmanu komplikacija koštanih metastaza. U dozi od 4 mg i.v. svake 3 do 4 nedelje smanjuje frakture kostiju i značajno smanjuje bol[6].
6. Kalcitonin – za sada postoji malo radova o upotrebi kalcitonina u terapiji bola kod koštanih metastaza i svi dosadašnji radovi govore da kalcitonin nema uticaj na kontrolu bola.
7. Hemoterapija – terapija bola putem hemoterapije ne pokazuje prednosti u odnosu na terapiju bola pomoću opioida i nema značajne razlike u preživljavanju, a znatno je skuplja. Očekivan odgovor u smislu smanjenja bola kod bolesnika sa koštanim metastazama je od 22–35%, a poboljšanje kvaliteta života se kreće od 13–22%, u zavisnosti od vrste primenjene hemoterapije[12].
8. Ostale terapije bola, kao što su nervni blokovi, retko se koriste.

Sistemska analgetska farmakoterapija (analgetske stepenice)

Koristi se u svim slučajevima kada primena prethodnih mera terapije karcinoma prostate, a samim tim i bola, nije dala rezultate u terapiji bola. Primenjuje se po svim pravilima „analgetskih stepenica" koje je preporučila Svetska zdravstvena organizacija[13].

Kompresija kičmene moždine

Ova komplikacija najčešće nastaje kao posledica frakture i kolapsa kičmenog pršljena ili zbog spoljne kompresije tumora koji prodire u spinalni kanal. Incidenca ove pojave kod bolesnika sa karcinomom prostate je manja od 10%. Kod onih kod kojih se desi kompresija, bol je prodromalni simptom u 96% slučajeva. Kompresija se najčešće javlja u torakalnom delu (70% slučajeva), a incidenca multiplih mesta kompresije je 18%. Trebalo bi uzeti u razmatranje hirurišku terapiju i radioterapiju. Primena kortikosteroida u smanjenju edema i terapiji bola je samo privremena[14,15].

Infiltracija jetre

Infiltracija jetre usled karcinoma najčešće dovodi do bola ispod desnog rebarnog luka, koji se širi u leđa i rame. Mehanizam nastanka bola je rastezanje nervnih završetaka u kapsuli jetre, iritacija dijafragme i krvarenje u nekrotičniom delu tumora. Bol kontrolišemo analgeticima, ali i primenom kortikosteroida. Koristi se i palijativna radioterapija, kao i intraarterijska hemoterapija i embolizacija unutar jetre[8].

Bol zbog primene terapije protiv karcinoma

Vidi se kao akutni bol kod primene oslobađajućeg hormona lutenizirajućeg hormona (LHRH). Simptomi se javljaju u prvoj nedelji ili poslednje 1–3 nedelje terapije. Javlja se kod 5–25% bolesnika kao egzacerebracija koštanog bola i kao urinarna retencija. Može se videti i kompresija kičmene moždine i iznenadna smrt. Uporedna primena androgen antagonista može da prevenira ove simptome. Vidi se i kao hronični bol tokom razvoja ginekomastije, a koja je komplikacija anti-androgene terapije karcinoma prostate[16].

Preporuke za terapiju bola kod bolesnika sa karcinomom prostate

Preporuke za terapiju bola kod bolesnika sa karcinomom prostate, prikazane u tabeli 3, date su na osnovu nivoa dokaza i stepena preporuke (tabele 4 i 5)[17].

TERAPIJA BOLA KOD BOLESNIKA SA KARCINOMOM PRELAZNOG EPITELA

Prema podacima Evropskog udruženja urologa, karcinom mokraćne bešike je sedmi najčešći karcinom koji se dijagnostikuje kod muškaraca, a jedanaesti ukoliko se posmatra kod oba pola zajedno. Karcinom prelaznog epitela (Transitional Cell Carcinoma – TCC) najčešći je karcinom mokraćne bešike i gornjeg urinarnog trakta. Mnogo

Tabela 3: Preporuke za terapiju kod bolesnika sa karcinomom prostate

Preporuke za terapiju	LE	GR
TERAPIJA BOLA		
Procena bola (lokalizacija, tip, jačina, sveukupni stres)		B
Bol zbog koštanih metastaza (jedna lezija)		
Spoljno zračenje	1b	A
Bol zbog koštanih metastaza (rasprostranjene)		
Primarna hormonska terapija	1a	A
Radioizotopi	2	B
Bol zbog metastaza (veći broj)		
Bisfosfonati	1b	A
Sistemska terapija bola		
WHO analgetske stepenice, stepenica 1: NSAID ili paracetamol	1a	A
Primena opioida		
Titriranje doze	2	B
Procena analgezije za proboj bola	1b	A
Triciklični antidepresivi i/ili antikonvulzivi u slučaju neuropatskog bola	1a	A

LE = nivo dokaza; GR = stepen preporuke

Tabela 4: Nivo dokaza[18]

Nivo (LE)	Vrsta dokaza
1a	Dokazi dobijeni metaanalizom ili iz randomiziranih studija
1b	Dokazi dobijeni iz bar jedne randomizirane studije
2a	Dokazi dobijeni iz jedne dobro dizajnirane kontrolisane studije bez randomizacije
2b	Dokazi dobijeni iz jedne dobro dizajnirane kvazieksperimentalne studije
3	Dokazi dobijeni iz jedne dobro dizajnirane neeksperimentalne studije, kao što je komparativna studija, korelacija ili prikaz slučaja
4	Dokazi dobijeni iz izveštaja nekog ekspertskog komiteta, mišljenja ili kliničkog iskustva uvaženih autoriteta

Tabela 5: Stepen preporuke[18]

stepen	Priroda preporuke
A	Bazirano na kliničkim studijama dobrog kvaliteta i konzistencije i uključuje najmanje jednu randomiziranu studiju
B	Bazirano na dobro povezanim kliničkim studijama, ali bez randomiziranih studija
C	Napravljene uprkos nedostatku direktno primenljivih kliničkih studija dobrog kvaliteta

češće se javlja u mokraćnoj bešici nego u bubrežnim čašicama i karlicama i u ureteru. Što se tiče bola, nema razlike između TCC i ostalih histoloških tipova urotelijalnih karcinoma. U mokraćnoj bešici bol obično započinje u vidu pečenja, zajedno sa nadražajnim simptomima, a u kasnijem stadijumu bolesti nastaje zbog invazije okoline ili metastatske invazije. TCC bubrežnog sabirnog sistema predstavlja oko 5–10% svih karcinoma bubrega i oko 5% svih TCC karcinoma urinarnog trakta. Kod TCC gornjeg urinarnog trakta bol predstavlja inicijani simptom u oko 30% slučajeva[19,20].

Mesto nastanka tumora i bol

Najčešći uzroci bola kod TCC mokraćne bešike su: opstrukcija gornjeg urinarnog trakta zbog rasta tumora blizu orificjuma uretera, invazija okoline i lokalno napredovanje tumora (karlični zid, nervni korenovi, drugi organi kao što su rektum i creva), koštane metastaze, tkivne metastaze.

Najčešći uzroci bola kod TCC gornjeg urinarnog trakta su: opstrukcija gornjeg urinarnog trakta (vidi se kod oko 30% slučajeva), akutna obstrukcija zbog koaguluma krvi, invazija okoline i lokalno napredovanje tumora (zadnji abdominalni zid, nervni korenovi, paraspinozni mišići, drugi organi, kao što su želudac, slezina i jetra), koštane metastaze, tkivne metastaze[21].

Bol zbog lokalnog širenja tumora

Bol zbog lokalnog širenja tumora mokraćne bešike dovodi do opstrukcije orificijuma uretera, distenzije uretera i hidronefroze praćene bolom (visceralni bol). Transuretralna resekcija tumora dovodi do otklanjanja opstrukcije i bola ili se to može uraditi i nefrostomijom. Infiltracija okolnih organa i nerava može da dovede do bola u vidu žarenja i pečenja (neuropatski bol). Taj bol je ponekad udružen sa parestezijama i motornim deficitom u donjim ekstremitetima. Opstrukcija limfnih sudova može da dovede do limedema donjih ekstremiteta i bola zbog distenzije mišićne fascije (somatski bol).

Hirurška intervencija je neophodna kod tumora mokraćne bešike i tumora gornjeg urinarnog trakta i najčešće dovodi do smanjenja ili nestanka bola. U uznapredovalim slučajevima, gde se koristi hemoterapija, može doći do smanjenja intenziteta bola i to kod onih bolesnika kod kojih se vidi smanjenje mase tumora (nivo dokaza 1a). Radioterapija se koristi za kontrolu lokalne progresije bolesti i pozitivno utiče na smanjene bola, ali može da dovede i do komplikacija, kao što su iritacija mokraćne bešike i proktitis (nivo dokaza 1a)[21].

Bol zbog metastaza

U uznapredovalim stadijumima TCC mokraćne bešike i TCC gornjeg urinarnog trakta često se vide hematogeno diseminovane metastaze u kostima. Radioterapija ima palijativnu analgetsku ulogu i najčešće se koristi 10 zračenja od 30–35 Gy. Kod 80–90% bolesnika dolazi do eliminacije bola (nivo dokaza 2b). Nema specifičnih studija za terapiju radioizotopima. Ortopedska i neurohirurška intervencija može da pomogne kod kompresije kičmene moždine i u stabilizaciji kičmenih pršljenova[21].

TERAPIJA BOLA KOD KARCINOMA RENALNIH ĆELIJA

Karcinom reanalnih ćelija (Renal Cell Carcinoma – RCC) najčešće se slučajno otkriva. Bol se javlja tek kada se tumor proširi unutar tkiva ili u okolinu i izazove opstrukciju protoka urina ili kada izazove krvarenje i formiranje krvnih ugrušaka. Oko 20–30% bolesnika u trenutku otkrivanja tumora već ima metastaze, a kod 30% se one jave tokom daljeg praćenja. To znači da oko 50–60% bolesnika sa RCC razvije metastaze i da je kod njih potrebno tretirati bol kao simptom. RCC se širi u pluća, kosti, mozak, jetru i u adrenergičke žlezde sa obe strane[22].

Mesto nastanka tumora i bol

Najčešći uzroci bola kod RCC su: invazija okoline i lokalno napredovanje tumora (zadnji abdominalni zid, nervni korenovi, paraspinozni mišići, drugi organi kao što su creva, jetra i slezina), opstrukcija gornjeg urinarnog trakta, koštane metastaze, tkivne metastaze.

Bol zbog lokalnog širenja tumora

Bolesnici sa tumorom koji vrši invaziju okoline imaju bolove. Hirurška metoda lečenja je najprihvatljivija i otklanja i bol. Ukoliko postoje metastaze, palijativna nefrektomija može biti indikovana kako

bi se sprečilo krvarenje, bol i paraneoplastični sindromi. Druga mogućnost je embolizacija tumora. Radioterapija nema uticaja na progresiju bolesti i na terapiju bola. Primena imunoterapije nije pokazala korist u terapiji bola, ali je njena primena zajedno sa palijativnom nefrektomijom pokazala veće prosečno preživljavanje bolesnika (17 meseci) u odnosu na samo izvedenu palijativnu nefrektomiju (7 meseci). (nivo dokaza 2b) Analgetska terapija i/ili palijativna drenaža urinarnog trakta treba da bude urađena kod bolesnika koji nisu podesni za operativno lečenje[22].

Bol zbog metastaza

Bolesnici sa koštanim metastazama imaju duže vreme preživljavanja (30 meseci) u odnosu na one sa visceralnim metastazama (11,6 meseci). Ukoliko bolesnik ima solitarnu metastazu koja može lako da se otkloni ili ukoliko ima izuzetno jake bolove ili patološku frakturu, onda treba da se preduzme hirurška intervencija. Posle hirurške intervencije dolazi do nestanka bola u oko 90% slučajeva (nivo dokaza 2b/3). Ukoliko postoji hipervaskularna koštana metastaza, embolizacija je jedna od terapijskih mogućnosti (nivo dokaza 3). Visoke doze zračenja bolnih metastaza su se u terapiji bola pokazale efikasnim u 50–75% slučajeva, ali nemaju uticaja na prognozu preživljavanja (nivo dokaza 2b)[9]. U malim studijama je dokazano da radionukleidi, kao što je stroncijum 89, mogu pozitivno da utiču na otklanjanje bola (nivo dokaza 3). Imunoterapija slabo utiče na koštane metastaze i nema uticaja na otklanjanje bola[22].

Ukoliko bolesnik ima metastaze koje nisu u kostima, onda je najbolja kombinacija hemoterapije i imunoterapije, a najbolje rezultate postiže kod metastaza u limfnim čvorovima i plućima. Smanjenje bola verovatno zavisi od odgovora na ovu terapiju, ali u radovima nema dokaza za ovu tvrdnju[23,24].

TERAPIJA BOLA KOD BOLESNIKA SA KARCINOMOM NADBUBREŽNE ŽLEZDE

Karcinom nadbubrežne žlezde je redak, ali ima veoma lošu prognozu. Sve promene koje su u dijametru veće od 5 cm trebalo bi hirurški otkloniti iako su neaktivne, zbog mogućeg nastanka maligniteta.

Feohromocitom predstavlja maligno tkivo koje nastaje u meduli nadbubrežne žlezde, paragangli-jama smeštenim uz aortu i ređe u simpatičkim ganglijama. Bolest se dobro leči sve dok ne metastazira. Karcinomi nadbubrežne žlezde najbolje reaguju na hormonsku terapiju. Bol koji je porekla tkivnih ili koštanih metastaza se najbolje tretira terapijskim dozama ^{131}J-MIBG (^{131}J-metaiodobenzylguanidine), ukoliko tkivo feohromocitoma preuzima ovaj radionukleid (nivo dokaza 2b). U literaturi nema dovoljno dokaza o efikasnosti upotrebe hemo i radioterapije u terapiji metastatskog feohromocitoma. Koristi se i simptomatska terapija bola.

Adenokortikalni karcinom ima izuzetno maligni potencijal i širi se lokalno i hematogeno. Metastazira najčešće u pluća (60%), jetru (50%), limfne čvorove (48%), kosti (24%), pleure (10%). Hemoterapija i radioterapija imaju mali efekat u lečenju[25]. Terapija bola zavisi od mesta nastanka bola. Abdominalni bolovi su tipični i oni se pre svega leče uporedo sa lečenjem osnovne bolesti, a to podrazumeva hirurško otklanjanje tumora. Koristi se i simptomatska terapija bola.

TERAPIJA BOLA KOD KARCINOMA PENISA

Karcinom penisa nije često oboljenje i u Evropi se javlja u incidenci manjoj od 2/100000 tokom godine. On predstavlja oko 1% svih karcinoma koji se javljaju kod muškaraca. Bol nije simptom koji karakteriše pojavu ovog karcinoma. Bol se može javiti i u ranim, ali i u kasnim fazama bolesti. U ranim fazama može doći do bola kao posledice subvezikalne opstrukcije i nemogućnosti pražnjenja bešike i tada je neophodno napraviti suprapubičnu drenažu kateterom i osloboditi bolesnika jakog bola. U kasnijim fazama bolesti javljaju se i metastaske promene, pre svega u ingvinalnim limfnim žlezdama. Bol je posledica lokalnog pritiska i invazije karcinoma, limfedema skrotuma i donjih ekstremiteta. Terapija bola pre svega obuhvata terapiju osnovne bolesti hirurški, hemoterapijom i palijativnom radioterapijom, kao i upotrebom sistemskih analgetika[26].

TERAPIJA BOLA KOD KARCINOMA TESTISA

Karcinom testisa se javlja najčešće u trećoj ili četvrtoj dekadi života. Bol se najčešće javlja u predelu samog testisa (20%), ali može da se širi u

Tabela 6: Efikasnost terapijskih opcija u otklanjanju bola kod karcinoma urogenitalnog trakta

Izvor bola	RCC	TCC	Pca	Karcinom penisa	Karcinom nadbubrega	Karcinom testisa
Terapijske opcije						
Koštane metastaze						
Hirurgija	+++	?	+	?	?	+
Radijacija	++	++	+++	?	+	?
Radionukleidi	+	?	+++	?	++	-
Hemoterapija	-	?	+	?	-	+++
Imunoterapija	-	-	-	?	?	?
Hormonska terapija	-	-	++	-	-	-
Analgetici	+++	+++	+++	+++	+++	+++
Infiltracija mekih tkiva						
Hirurgija	+++	+++	-	?	?	+
Radijacija	-	+	++	?	+	?
Hemoterapija	+	++	+	?	++	+++
Imunoterapija	+	-	-	?	?	?
Hormonska terapija	-	-	++	-	-	-
Analgetici	+++	+++	+++	+++	+++	+++
Kompresija ili infiltracija nerva						
Hirurgija	+++	+++	++	?	?	++
Radijacija	+	+	++	?	+	?
Hemoterapija	+	++	+	?	?	+++
Imunoterapija	+	-	-	?	?	?
Hormonska terapija	-	-	++	-	-	-
Analgetici	+++	+++	+++	+++	+++	+++

TCC = karcinom prelaznog epitela; RCC = karcinom renalnih ćelija; Pca = karcinom prostate; ? = nema dokaza u literaturi; + = slaba kontrola bola; ++ = umerena kontrola bola; +++ = dobra kontrola bola; - (minus) = ne utiče na bol

prepone ili slabine, pa čak i u leđa (11%). Bol koji je porekla karcinoma testisa najbolje se leči u sklopu lečenja osnovne bolesti, operativnim uklanjanjem obolelog testisa. Slabinski bol koji nastaje zbog retroperitonealnih metastaza u limfnim čvorovima polako se smanjuje usled dejstva hemoterapije i smanjenja tumorske mase (nivo dokaza 2b). Retroperitonealne mase mogu da izazovu opstrukciju uretera i bol zbog hidronefroze, pa terapija podrazumeva primenu uretralnog stenta ili perkutanu nefrostomiju. Bol kao posledica koštanih metastaza ili kompresije kičmene moždine je veoma redak i tretira se hemoterapijom, palijativnom radioterapijom i sistemskim analgeticima[27,28].

U tabeli 6 je prikazana efikasnost pojedinih terapijskih opcija u otklanjanju bola kod karcinoma urogenitalnog trakta.

Zaključak

Terapija hroničnog kancerskog bola kod uroloških bolesnika predstavlja veliki izazov, usled različitih vrsta karcinoma koji nastaju u urotraktu i njihovih specifičnosti. Loša terapija bola ima

razarajuće posledice koje ozbiljno utiču na kvalitet života ovih bolenika, umanjuju njihovu funkcionalnost i ostavljaju ogroman emocionalni teret kako na bolesnika tako i na njegovu porodicu. Kao i kod svake vrste hroničnog bola, prilaz pacijentu sa urološkim kancerskim bolom treba da bude individualan, uzimajući u obzir osobine samog pacijenta, kao što su godine starosti, prisustvo komorbiditeta, funkcionisanje pacijenta, prethodna upotreba opioida i drugih lekova, kao i stadijum maligne bolesti, njegove osobine da se širi lokalno i daje udaljene metastaze, intenzitet bola koji izaziva. Multimodalna strategija lečenja kancerskog bola je i danas najuspešnija.

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Case report

PRACTICING OPIOID-FREE ANESTHESIA FOR LAPAROSCOPIC CHOLECYSTECTOMY OPIOID-FREE ANESTHESIA

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Abstract

***Introduction**: Opioid free anesthesia (OFA) is an anesthesiological technique, which uses non-opioid analgesics, such as paracetamol, dexamethasone, lidocaine, ketamine, and magnesium sulfate instead of opioids. In this case, the report about patient who after previous surgeries experienced opioid side effects is followed by a narrative review; we present the OFA method for laparoscopic cholecystectomy. **Case report**: We present a case of a 55-year-old woman with a history of controlled hypertension and asthma, planned for laparoscopic cholecystectomy. Previously she underwent two surgical interventions; bilateral radical mastectomy performed separately with a three year gap. Both anesthesias were complicated, postoperatively with nausea, vomiting, dizziness, and respiratory depression. Based on the previous postoperative complications, we hypothesized that nausea, vomiting, dizziness, and respiratory depression were caused by opioids, and we decided to perform OFA. Before the induction the patient received dexamethasone 8 mg and paracetamol 1 gr intravenously, followed by induction with midazolam 3 mg, lidocaine hydrochloride 78 mg, propofol 160 mg, ketamine hydrochloride 39 mg and rocuronium bromide 60 mg. After tracheal intubation, continuous intravenous infusion with lidocaine hydrochloride 2 mg/kg/hr and magnesium sulfate 1.5 gr/hr was started. Anesthesia was maintained by using sevoflurane MAC 0.7–1. At the end of the surgery, 2.5 gr of metamizole was given intravenously. Postoperative recovery was uneventful. **Conclusion**: In our patient, OFA eliminated opioid-related side effects (nausea, vomiting, dizziness, and shortness of breath), and provided satisfying postoperative analgesia.*

***Keywords:** opioid free anesthesia; laparoscopic cholecystectomy; pain; nausea vomiting*

Introduction

The opioid-free anesthesia (OFA) technique is characterized by perioperative opioid omittance[1]. Although opioids are still the mainstay analgesics used for the treatment of moderate to severe pain, opioid avoidance leads to less opioid-related side effects in the postoperative period, such as respiratory depression, postoperative nausea, and vomiting (PONV), dizziness, and constipation. We present a case of a patient with previous experience of opioid-mediated side effects, who underwent laparoscopic cholecystectomy with perioperative OFA application.

Case report

A 55-year-old woman (height 165 cm, weight 78 kg) was scheduled for laparoscopic cholecystectomy under general anesthesia. The patient had a history of hypertension treated with an angiotensin converting enzyme inhibitor and asthma which was treated with a bronchodilator (aminophylline). The patient had a bilateral mastectomy, left radical mastectomy was done five years before and right radical mastectomy two years before. After previous surgeries, postoperative recovery was complicated with nausea, vomiting, dizziness and respiratory depression (SpO_2 was 88–90% with an oxygen mask and respiratory rate of 8 breaths per minute), which necessitated the intensive care unit

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admission. The decision was made that for this surgery, an OFA technique is suitable. The day before surgery, the patient was trained to use the Numeric Rating Scale (NRS) score (0 means no pain at all, and the number 10 means the worst imaginable pain).

The patient was premedicated with 5 mg of diazepam orally two hours before the operation. In the operating room, the patient was placed on continuous hemodynamic monitoring, including electrocardiography (ECG), heart rate (HR), non-invasive blood pressure measurement (NIBP) every 5 minutes, saturation with oxygen by pulse oximetry (SpO_2%) and capnography. The preinduction vital signs were: NIBP: 157/92 mmHg, HR: 88/min, RR: 16/min, SpO_2 = 93%. Before the induction to general anesthesia, dexamethasone 8 mg as an antiemetic agent and paracetamol 1 gr intravenously (i.v.), were given. The induction into general anesthesia included midazolam 3 mg, lidocaine hydrochloride 78 mg, propofol 160 mg, ketamine hydrochloride 39 mg, and rocuronium bromide 60 mg. After tracheal intubation continuous intravenous infusion of lidocaine hydrochloride 2 mg/kg/h was started, and magnesium sulfate ($MgSO_4$) 1.5 gr/h. Anesthesia was maintained by using sevoflurane MAC 0.7–1 to maintain mean arterial pressure with a value of +/- 20% of the baseline value. The patient was mechanically ventilated with PCV-VG ventilation mode, with a breath volume of 6–8 ml/kg from a mixture of gases in proportion to 50% oxygen and 50% air, I:E ratio = 1:2, the number of respirations were customized according to $EtCO_2$ between 35–45 mmHg, PEEP 5 cm H_2O. An oral-gastric tube and sequential compression device were placed, and normothermia was maintained with a warming blanket. During the laparoscopy, the intra-abdominal pressure was 12 mmHg with continuous insufflation of CO_2. The operation lasted for one hour and was uneventful. After the gallbladder removal, the continuous infusion of lidocaine and magnesium sulfate was discontinued, and 2.5 gr of metamizole was given intravenously. At the end of the operation, the gastric tube was removed, and the residual neuromuscular blockade was antagonized with neostigmine 0.05 mg/kg and 0.02 mg/kg of atropine i.v. And the patient was extubated.

The patient was pain-free (VAS score 1), no nausea, vomiting, or dizziness complaining. She was transferred to the PACU and stayed there for 60 minutes. Postoperative analgesia plan included 1g of paracetamol for NRS score from 4 to 6, or 100 mg of tramadol for NRS score from 7 to 10, while ketonal 100 mg was used as a rescue analgesic. The pain at rest and on movement and PONV were recorded at 1, 4, 8, 12, and 24 hours after the surgery. One hour after the surgery, the patient reported pain on NRS to score one at rest, and NRS score two on movement, no PONV, no respiratory depression or dizziness. She said that she felt very good like she wasn't operated and she was transferred to the ward. Postoperative pain was well controlled with NRS score 2 at rest, and NRS score 3 on movement at the fourth hour, and NRS score 3 at rest, and, NRS score 3 on movement on the eighth hour, without PONV. Paracetamol 1 gr was used for the pain management following 12 hours and 24 hours (NRS score 5 at rest, and NRS score 6 on movement and NRS 3 at rest and NRS 4 on movement, respectively), without PONV. Patient felt very comfortable during her stay in the hospital; she slept well without nightmare complaints.

Discussion

Here we present the case of a patient who was perioperatively managed with OFA as an example that this method is reasonably used in patients with previously experienced opioid's side effects. Although opioids are the strongest analgesics and an essential part of most general anesthesias, they have numerous side-effects, short and long term consequences[2], including respiratory depression[3], nausea[4], vomiting[5], dizziness[6], sedation[7], ileus[7], delirium[8], pruritus[4], urinary retention[7], hyperalgesia[7,9], opioid tolerance[7], opioid-induced immunosuppression[10], and sleep disorders[11].

Opioids can be avoided by intraoperative using multi-modal non-opioid analgesics such as paracetamol, dexamethasone, lidocaine, ketamine and magnesium sulfate, medications acting on receptors centrally and peripherally in the pain pathway[12]. Paracetamol given before the induction to anesthesia leads to lower requirements of opioids during the operation[13]. Dexamethasone has effective antiemetic effects given in a lower dose. Moreover intermediate doses (0.1–0.2 mg/kg) of dexamethasone have an opioid-sparing effect and has bene-

ficial effects on postoperative pain[14]. Lidocaine is local anesthetic and has an analgesic, antihyperalgesic and anti-inflammatory effect, and given intravenously reduces perioperative opioid consumption, provides better pain control and faster return of the bowel function[15]. Ketamine is a unique intravenous anesthetic with an analgesic effect, opioid-sparing effect, acting on N-methyl D-aspartate (NMDA) receptors through blocking potassium to exit outside of the cell[16]. Magnesium sulfate acts on NMDA receptors by blocking the entrance of calcium and sodium inside the cell and given as a continuous infusion in the intra-operative period leads to low pain scores and less nausea and vomiting in the postoperative period[17]. The occurrence of PONV after laparoscopic cholecystectomy ranges from 46% to 75%[18]. Apfel et al. created risk score for PONV with an aim to implement preventive strategy for PONV[19]. This score is consisted of four highly predictive risk factors: female gender, non-smokers, history of previous PONV or motion sickness and expected administration of postoperative opioids. Dexamethasone given in intermediate doses (0.1–0.2 mg/kg) has antiemetic effects, and better efficacy if given preventively[20]. It is also indicated in patients with asthma because it improves the efficacy of bronchodilator therapy[21]. Ketamine also has a bronchodilator effect and is suitable for induction and maintaining of anesthesia in patients with asthma[22]. Anesthetics dose of ketamine has an emetic effect and leads to nausea, but sub-anesthetic dose (< 0.5 mg/kg) reduces nausea and vomiting, probably because of his opioid-sparing effect[23]. The strategies for PONV reduction are regional anesthesia and total intravenous anesthesia – TIVA with propofol[24], volatile anesthetics avoidance, or use of sevoflurane and desflurane[25], adequate hidration[26], administration of dextrose[27], multimodal postoperative pain control (using regional anesthetic techniques, paracetamol, NSAID, other non-opioid adjuvants)[28], administration of antiemetics[29]. Pre-operative administration of midazolam in dose 0.04 mg/kg has shown significantly reduced PONV in the first 24 hours after intra-abdominal or ambulatory surgery[30].

In the postoperative period, the patient was treated according to hospital protocol for postoperative analgesia with the total amount of given analgesics of 2 gr paracetamol during 24 hours after the surgery. Antiemetics and analgesics (tramadol and ketoprofen as a rescue analgesic) were not given during the post-operative period. No side effects were recorded during the postoperative period. Usually suggested medications for opioid-free anesthesia like alfa-2 agonists (clonidine and dexmedetomidine) were not registered in our country and therefore not used[2,12]. This case can serve as an example of OFA approach. Alfa-2 agonists have many pharmacological characteristics such as sedation, hypnosis, anxiolysis, analgesia, and sympatholysis.

OFA is indicated in patients with acute and chronic opioid addiction. It can be used in opioid-tolerant patients: patients with persistent non-cancer pain, cancer pain, a substance abuse disorder, and with acute opioid tolerance. Opioid-addicted patients planned for surgery have 30–100% increased intra-operative opioid requirements, compared to opioid-naive patients[31]. OFA is also indicated to avoid administration of opioids during the perioperative period.

Also, OFA can be used in obese patients scheduled for bariatric surgery, therefore serves for avoiding opioids as this group of patients are particularly in risk to develop respiratory depression[32]. Majority of obese patients have obstructive sleep apnoea syndrome (OSA) and they are prone to airway obstruction and desaturation in the perioperative period, especially if opioids are given. Mulier et al. evaluated the effect of OFA versus general opioid anesthesia in patients scheduled for elective laparoscopic bariatric surgery[2]. Patients who received OFA required fewer analgesics in the postoperative period, experienced less postoperative PONV and shivering, less postoperative hypertension and desaturation, and had an improved quality of recovery after surgery.

Samuels et al. compared postoperative opioid consumption in three groups of patients divided into three anesthesia regiments: the first group received opioid-sparing anesthesia (OSA), the second group received opioid-free anesthesia (OFA), and the third group received opioid anesthesia (OA)[12]. These patients were planned for various surgical procedures, including breast reconstructions, cochlear implants, stapedectomies, and mastoidectomies. In the postoperative period, 73% of the OFA patients didn't require opioids, compared to 52% of OA patients and 37% of OSA patients. OFA patients also had less nausea and vomiting compared with OSA and OA patients. OFA also

reduces PONV compared to patients who underwent general anesthesia with volatile anesthetics and opioids[33].

Additionally, cancer patients can benefit from OFA is also indicated in patients scheduled for cancer surgery opioids have immunosuppressive effects (inhibition of cellular immunity), and potentially can stimulate cancer cells growth and angiogenesis[34].

Based on the literature data, OFA is suggested for obese patients, patients with OSA, pulmonary disease (asthma, COPD, respiratory insufficiency), history of acute or chronic opioid dependence, hyperalgesia, history of chronic pain, immunodeficiency, oncologic surgery, and inflammatory diseases. Absolute contraindication for OFA is an allergy of any non-opioid adjuvant drug, while relative contraindications are cerebrovascular disease, disorders of autonomic failure, acute coronary ischemia, critical coronary stenosis, heart block, extreme bradycardia, non-stabilized hypovolemic shock, polytrauma patient, elderly patients on beta blockers.

Opioid-free postoperative analgesia has opioid-tolerant more than ten years[35], and the POFA trial is the first prospective, randomized, multicentric study evaluating the effects of OFA on severe postoperative opioid-related adverse events[36].

Conclusion

Opioid-free anesthesia technique leads to less opioid-related side effects such as PONV, dizziness, respiratory depression, and more satisfied patient. It's a safe and effective anesthetic technique, suggested for ambulatory surgery.

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Review article

ANTICOAGULATION DURING CONTINUOUS RENAL REPLACEMENT THERAPY: AN UPDATE.

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Abstract

Renal replacement therapy in Intensive Care Units is a daily practice worldwide. Ensuring blood flow continuum within extracorporeal circuit is one of the basic tasks during therapy. Unfractionated heparin remains the most popular anticoagulant used. Alternatives, such as low molecular weight heparins, prostacyclin, fondaparinux, or regional use of citrate or nafomostate mesilate are also gaining ground, mainly due to their safety profile. Still, there is no worldwide consensus about their use. Systemic, regional, combined or no coagulation at all; the final choice depends on the patients' characteristics and co-morbidities, as well as institutional and organizational protocols, equipment availability and staff education. This article presents a review of the current modalities for anticoagulation during continuous renal replacement therapy.

Keywords*: anticoagulation; continuous renal replacement therapy*

Introduction

Acute renal dysfunction is substantially contributing to morbidity and mortality among critically ill patients[1]. In the intensive care unit (ICU) renal replacement therapy (RRT) has proven its role in the management of patients with – acute and chronic- renal failure; although reports about long-term outcome of these patients are controversial[2,3].

RRTs include intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapies (CRRTs), and hybrid therapies such as prolonged intermittent renal replacement therapies (PIRRTs), which provide prolonged but still intermittent dialysis. Narrower terms used to describe PIRRT include sustained low-efficiency (daily) dialysis (SLEDD), sustained low-efficiency (daily) diafiltration (SLEDD-f), extended daily dialysis (EDD), slow continuous dialysis (SCD), go slow dialysis, and accelerated venovenous hemofiltration (AVVH)[4,5].

In general, RRT therapy is chosen based upon the patients' characteristics and institutional availability. In the dynamic ICU environment, CRRTs are the most popular type of RRT, as it is related to fewer episodes of hemodynamic instability and better control of fluid balance[6].

One of the most essential issues during CRRT is ensuring continuous extracorporeal blood flow without clotting, both within the circuit (especially in central venous catheter for RRT) and the artificial filter. However, anticoagulation strategy during CRRT needs special attention and balancing between the life of the artificial extracorporeal circuit and the danger for patient bleeding[7,8].

The current article provides a review of the literature about the methods of anticoagulation during CRRT.

Unfractionated Heparin

Unfractionated heparin (UFH) is a heterogeneous mixture of glycosaminoglycans with molecular weight 5000–30000 Daltons kiloDaltons. It acts by forming a complex with antithrombin III (ATIII), catalyzing the inhibition of several activated (a) blood coagulation factors: thrombin (factor IIa),

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Christmas factor (FIXa), Stuart factor (FXa), plasma thromboplastin antecedent (factor XIa) and Hageman factor (FXIIa)[7]. UFH is metabolized by the liver and metabolites are excreted by the kidneys. Heparin is heterogeneous in regard not only to its molecular weight but also to its anticoagulant effects and its pharmacokinetics. Its half life is dose-dependent ranging from 30 to 180 minutes[9]. However, it is considered as the classic choice for anticoagulation during CRRT, mainly because of its low cost, high availability and ease of administration[10,11].

Dosing of UFH during CRRT is usually based on measured activated partial thromboplastin time (APPT) or activated clotting time (ACT). The target treatment for APPT ratio is between 1.2–1.5 and 120–180 sec for ACT[6,7].

In practice, development of local (bedside) protocols should be used. Each protocol includes every aspect of UFH anticoagulation during CRRT and incorporates possible local characteristics (institutional, organizational). Key points in every protocol: 1) the need or not for priming the circuit before initiation of therapy, 2) starting dose, 3) monitoring parameters, measuring interval and target, 4) modification of dose, 5) other (e.g. handling complications and emergencies). A parallel quality assurance strategy (staff education, assessment meetings, etc.) should also be in place. In general, a filter life of 20–24 h is common when a UFH anticoagulation protocol is „working".

A simple example of such protocol is displayed table 1.

Despite its popularity, UFH should be administered with caution during CRRT. First of all, because the basic assay for monitoring UFH therapy (APPT) is just a surrogate marker for estimation of heparin concentration, which is susceptible to several cofounding factors[11]. In other conditions, like deep venous thrombosis, weight-based nomograms have been suggested in order to overcome difficulties delivering UFH[12]. Yet, in CRRT several authors claim that Anti-Factor Xa (anti- FXa) levels may provide better and more reliable monitoring; however, even these levels show considerable inter-laboratory variation, and there are insufficient clinical studies proving improved clinical efficacy[14–16].

The above creates additional problems in a seemingly simple problem: UFH reversal. Protamine dosing is generally 1–1.5 mg per 100 UI of Heparin, yet time elapsed from heparin administration modifies the regiment to 0.5–0.75 mg / 100 units UFH if 30–120 min has passed, or 0.2–0.375 mg/100 UI UFH, if time elapsed is > 2 h. APPT should be monitored 5–15 min after dose and then every 2–8 h[17]. Some authors suggest an alternative to sole UFH protocol, with Heparin administration (at 1000 UI/h) prefilter and protamine administration (at 10 mg/h or 1:100 ratio) postfilter into venous chamber or directly into the return limb of the access catheter (via a suitable Y piece, but not a three-way tap)[18]. In any case, attention is needed because protamine can trigger serious adverse effects, such as anaphylactoid reactions, hypotension and catastrophic pulmonary vasoconstriction[19].

Along with that, UFH use is not without complications. Bleeding, defined as a decrease in hemoglobin ≥ 1.5 gr/dl, below the level at initiation of CRRT often leads to transfusion of one or more units of red

Table 1. An example of UFH CRRT protocol (authors' protocol).

APTT (seconds)	Bolus dose	Rate change
<40	1000-2000 UI*	+200 UI/h (do not exceed 20UI/kg/h)
40.1-45	Nothing	+100UI/h (do not exceed 20UI/kg/h)
45.1-55	Nothing	No change
55.1-65	Nothing	Stop 30 min and -100 UI/h
>65	Nothing	Stop 1h and -200UI/h

**UI: International Units*
Heparin solution: 1ml of 10000 U/ml of UFH in 19 ml of NaCl 0.9% (500U/ml)
Initial bolus 20 UI/kg, followed by infusion of 5 UI/kg/h
Monitoring APTT/ 4h

blood cells[20]. In case of increased (bleeding) risk, higher circuit blood flow is recommended[21].

Heparin-induced thrombocytopenia (HIT) is heparin's most clinically relevant non hemorrhagic complication. HIT Type I caused direct effect of heparin on platelets and HIT II is caused by antibodies to complexes of platelet factor 4 (PF4) and heparin[22]. In patients in CRRT, HIT II is usually observed[23]. Clinically, thrombocytopenia with both arterial and venous thrombosis is the main feature of HIT II[20]. Additionally, recent reports suggest that CRRT *per se* may also be a thrombocytopenia-related factor[24]. Regardless of the latter, HIT probability should be calculated in all patients before CRRT, either via 4Ts Score or by newer HIT Expert Probability (HEP) score. While the 4Ts score system calculates the risk for HIT after considering selected parameters (Table 2), the HEP score uses more variables such as skin necrosis, acute skin reaction and the presence of bleeding[25].

In general, patients with a baseline APPT > 55 sec, platelet count < 40000/mm^3, allergy in heparin, prior history of heparin induced thrombocytopenia or high 4Ts or HEP score, incident of intracranial or gastrointestinal hemorrhage within the previous three months, active bleeding or significant trauma within 3 days and evidence of irreversible coagulopathy because of liver failure should not receive heparin during CRRT[26].

Other side effects of UFH are hypertriglyceridemia (releases and depletes endothelium-bound lipoprotein lipase), osteoporosis and hypoaldosteronism[10]. Furthermore, it should be kept in mind that conditions, like sepsis or systemic inflammation, require special caution due to reduction of ATIII concentration as a result of its consumption or proteolytic degradation[27]. In the latter, an ATIII supplementation protocol has been suggested. The supplementation protocol aims to achieve a plasma ATIII level greater than 110 to 120%. Each time that ATIII activity drops below 70% (measurement before CRRT), 50 UI/kg ATIII is administered intravenously. The fixed daily 50 UI/kg dose regimen of ATIII supplementation is chosen because of the 1.7% per UI/kg AT response and a mean half-life of 18.9 hours are expected in these patients, as reported[28,29].

Low Molecular Weight Heparins

During the last decades, low molecular weight heparin (LMWHs) are replacing UFH as anticoagulants in CRRT. This increasing tendency, despite

Table 2. HIT score. Applying the scoring system to suspected patients produces a totalled score between 0 and 8. Scores of 0 to 3, 4 to 5, and 6 to 8 are respectively classified as low, moderate, and high probability for HIT.

Points	2	1	0
Thrombocytopenia	>50% fall or PLT nadir $>20 \times 10^9$ L^{-1}	30-50% fall or PLT nadir 10-19 $\times 10^9$ L^{-1}	<30% fall or PLT nadir 10×10^9 L^{-1}
Timing of PLT fall	Clear onset between days 5 and 10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days	Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts) or onset after day 10 or fall ≤ 1 day (prior heparin exposure 30–100 days ago)	Platelet count fall < 4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or nonnecrotizing (erythematous) skin lesions or suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

the higher cost, could be attributed to the clinical benefits of LMWHs over UFH (Table 3).

Their longer half-time, low affinity to endothelial cells, plasma proteins, macrophages and ab-

Table 3. Comparative statements between UFH and LMWHs[9,10,30,31].

Characteristic	UFH	LMWHs
Availability for antithrombin reaction	30%	>85%
AntiXa/AntiIIa ratio	1:1	>2-9.7:1
Molecular weight-(MW) (kDa)	15 (4-30)	4.5 (2-10)
Half-time ($T_{1/2}$)	Short (~1h, dose-dependent)	Longer, more predictable
Bioavailability	Low	Higher than UFH
Dosage regiment	Frequent	Less frequent
Clearance	Hepatic	Renal
Bleeding tendency	High	Lower than UFH
Thrombocytopenia	High	Lower than UFH
Osteoporosis propensity	High	Lower than UFH
Therapeutic response	Variable	Predictable
Reversal	Fully with protamine	Partially with protamine
Laboratory monitoring	Essential	See text for monitoring*

LMWHs are produced by depolymerization of the long oligosaccharide chains of UFH into smaller chains. The different depolymerization methods (chemical or enzymatic β-elimination, oxidative cleavage or nitrous depolymerization) result in LMWHs with distinct characteristics (Table 4).

Tests for monitoring LMWH*'s* include anti-factor Xa (anti-FXa), activated partial thromboplastin time (APTT) and thrombin generation. Since they have predominantly anti-FXa activity, it is appropriate to monitor their levels by an anti-FXa chromogenic assay[39] (detection limit of 0.01 UI/ml). Therapeutic levels are defined as 0.5–1 UI/ml and levels below 0.5 UI/ml are considered insufficient, while above 1 UI/ml are considered excessive anticoagulation[39–41]. Thrombin generation with tissue factor-rich activator is an alternative promising method for monitoring LMWHs[42].

Heparin complications (Bleeding, HIT) can also be triggered by LMWHs, although less often and in milder forms[10]. In case of hemorrhage due to overdose, protamine is not as efficient as in UFH overdose and fresh frozen plasma (FFP) or recombined activated factor VII (rFVIIa) may be needed[43].

sence of clearance by the different modes of RRT, allow for one single bolus dose at start of therapy, in case of intermittent hemodialysis or PIRRT[8]. For CRRT, the most adopted strategy most is either an initial bolus followed by a continuous infusion or intermittent boluses every 6 hours[46]. An alternative regimen is to omit the loading dose and simply start with a continuous intravenous infusion (civ) (Table 5).

Dermatan sulfate

Dermatan sulfate is a natural heparinoid that also has been used for CRRT anticoagulation. It acts by selectively inhibiting thrombin and it does not inhibit factor Xa and does not interfere with platelets. Dosing include a bolus loading of 150 mg followed by an infusion of 12–13 mg/h[52]. Measuring APPT is suggested as monitoring method.

Table 4. Comparative table of LMWHs[32-39].

	MW (kDa)	$T_{1/2}$ (h)	Bioavaibility (%)	AntiXa/AntiIIa ratio	AntiXa activity (UI/mg)
Nadroparin	4.3	3.7	89	3.5	100
Enoxaparin	4.5	4.5	90-92	3.8	100
Dalteparin	6	3-5	87	2.7	156
Bemiparin	3.6	5.1	96	8.1	110
Certoparin	5.4	6	>90	2.4	
Parnaparin	5	4	~100	2.3	
Reviparin	4.4	3	95	4.2	124
Tinzaparin	6.5	3.4	87	2.8	100
Ardeparin	5.5-6.5	3.3	92	1.7-2.4	

Table 5. Examples of LMWHs used for CRRT.

LMWH used	Initial bolus	Maintenance dose	Anti FXa –level activity (UI/ml)	Monitoring interval
Enoxaparin [44]	0.15 mg/kg	0.05 mg/kg/h	0.25-0.3	6h
Enoxaparin [45]		0.5-0.7 mg/kg/12h	0.5-1	12h
Enoxaparin [46]		1.5mg/kg per 24h	0.07-1.26	6h
Enoxaparin [47]	0.5 mg/kg	1mg/kg/day	0.29	
Tinzaparin [48]		400-800 UI/h	*	*
Nadroparin [49]	0.6 ml	0.3 ml/4h	*	*
Dalteparin [50]		600 UI/h	0.3-08	*
Dalterparin [51]	2000 UI	320 UI/h	0.5-1	*

**not available*

Danaparoid

Danaparoid is a low molecular weight (5 kDa) heparinoid glycosaminoglycuronan antithrombotic agent that contains a mixture of heparan sulfate (84%), dermatan sulfate (12%) and chondroitin sulfate (4%). It acts mainly via ATIII and on factor IIa (Anti-Xa / Anti-IIa activity ration > 20:1)[53]. In CRRT, it has been used in patients with high risk of HIT in the following dosing regiments: 1) 750UI loading bolus followed by 50-150UI/h civ or 2) 3500 UI bolus followed by 100 U/h civ, aiming at anti-Xa levels of 0.5–0.7 U/ml[54,55].

Fondaparinux

Fondaparinux is the only synthetic pentasaccharide factor Xa inhibitor (Table 5) that has been used in CRRT.

Yet, data are limited to case reports or case series. In such a case (patient with HIT type II), dosing regimen of 2.5 mg instilled directly into the dialysis circuit was chosen[57]; while in case of RRT (Intermittent Hemodialysis), fondaparinux 0.05 mg/kg actual body weight was administered on days of dialysis. Dosing was increased to a maximum dose of 0.08 mg/kg actual body weight based on anti-factor Xa levels[58]. Still, the optimal fondaparinux dosage remains unknown. Thus, peak

Table 6. Comparative table of synthetic Factor Xa inhibitors[56].

	Fondaparinux	**Idraparinux**	**Idrabiotaparinux**
Bioavailability	100	100	100
Half-life	17-21 hours	80-130 hours*	60 days
Dose	2.5-10 mg	2.0 mg	3.0mg
Elimination	Renal	Renal	Renal
Antidote	No	No	Avidin

**can be increased to 600 hours in subsequent dosing*

anti-factor Xa concentrations may be essential for guiding therapy[59].

Hirudin, Lepirudin and Bivalirudin

Hirudin and it analogs, lepirudin (recombinant hirudin) and bivalirudin, act independently of PF4 and cofactors; thus has been used as an alternative in patients with HIT[60–66]. For CRRT, lepirudin is administered either as a continuous infusion (0.005–0.01 mg⁄kg⁄h) or delivered in bolus doses (0.2 mg⁄kg); while bivalirudin is administered pre-filter in 0.009–0.023 mg/kg/h (1–2.5mg/h)[62–66]. Although, APPT can be used as monitoring tool (aiming at 1.5–2.5 times baseline), there is no linear correlation with anticoagulation activity. Instead specialized tests such as ecarin clotting time (ECT) or hirudin ELISA have been suggested. Target for ECT during CRRT is 80–100 sec[64]. In case of bleeding, no antidote exists and rFVIIa or FFP may be needed. Yet, in general, results from its use in CRRT are comparable with UFH protocols[67–69].

Argatroban

Argatroban is a monovalent direct thrombin inhibitor (DTI) with hepatic metabolism and a short half time (35 min). Although it does not require a dosage adjustment in patients with renal dysfunction or in patients undergoing RRT, up to 22% of the drug is renally excreted; thus, caution is needed[70]. Half time may increase to 2.7 in cardiac surgical critical ill patients with HIT[71]. Monitoring is usually achieved via APTT or activated clotting time (ACT) measurements; although recent studies suggest thrombin time (TT) and rotational thromboelastometry (ROTEM) as better alternatives[72]. Data about dosing vary: 1) initiation at 0.2 μg/kg/min at up to 3.1 μg/kg/min in accordance to APTT[73] 2) start at 0.5 μg/kg/minute, and adjustment in 0.1–0.25 μg/kg/minute increments[71] or 3) a loading dose of 100 μg/kg followed by a maintenance infusion rate (μg/kg/min), which can be calculated from the scores as follows: for Acute Physiology and Chronic Health Evaluation (APACHE)-II: 2.15–0.06 x APACHE II; for Simplified Acute Physiology Score (SAPS) II: 2.06–0.03 x SAPS II; and for indocyanine green plasma disappearance rate (ICG-PDR): -0.35 + 0.08 x ICG-PDR[74].

Oral Direct thrombin inhibitors, Direct factor X inhibitors and Warfarin

This group includes the oral DTI dabigatran and the factor X inhibitors apixaban, rivaroxaban and edoxaban. Given the need for oral access without the current ability to assess adequate absorption and level of anticoagulation with these drugs, this is likely to limit their use in CRRT[75]. Although vitamin K antagonist warfarin has been studied in intermittent hemodialysis, there are no data for use in CRRT[76–78].

Tirofiban

Tirofiban, an antiplatelet agent, is the only glycoprotein IIB/IIA inhibitor (the group includes also abciximab and eptifibatide) used in RRT. Tirofiban in dose regiment 0.2 μg/kg/min bolus over 30 min followed by 0.05 μg/kg/min civ. has been used in conjunction with UFH (APTT target 2–3 times normal range) in patients with cardiogenic shock and acute kidney injury requiring CRRT[77].

In polimixina-B hemoperfusion a loading dose of 250 μg/kg has also demonstrated good results[80].

Prostacyclin

Prostacyclin (PGI_2) and other prostanoids have been used alone or in combination with UFH and LMWHs in CRRT[81]. Whereas their vasodilatating effect lasts for 2 minutes, their antiplatelet effect continues for over 2 hours. Dosing in CRRT is 4–10 ng/kg/min civ. Limiting hypotension is achieved either by titrating to 0.5 ng/kg/min at the initiation of therapy or by restricting infusion at extracorporeal circuit only[81]. Other side effects include minimal increase in intracranial pressure (especially in hepatic failure), nausea, vomiting, chest pain, anxiety, bradycardia, tachycardia, dyspnoea, abdominal pain and ventilation perfusion mismatch (clinically significant in those with reflex hypoxic pulmonary vasoconstriction). ROTEM can be used in monitoring of anticoagulant effect[82]. Apart from hypotension and difficulty of monitoring, PGI_2 cost is another drawback for its wider application.

Nafomostate mesilate

Nafomostate mesilate (NM) is a synthetic proteinase inhibitor with short half life (5–8 min). It acts on plasmin, trypsin, kalikrein, thrombin, factor Xa and XIIa and tissue factor-factor VIIa complex. It has no antidote and serious side effects include agranulocytosis, hyperkalemia and anaphylactoid reactions[83]. Yet, the use of NM as an anticoagulant during CRRT is associated with decreased incidence of bleeding complications compared with the use of UFH[84]. Data about its use in CRRT comes mainly from Japan, where it is the most frequent CRRT anticoagulant[85]. Filter is primed with 500 solution of NaCl 0.9% with 20 mg NM and then a maintenance infusion of 10–30 mg/h is administered[86]. Monitoring is performed via APTT or ACT[87].

Citrate anticoagulation

Citrate is a small (191 Da) negative charged molecule that acts by forming citrate-calcium (ionized-iCa) complexes, thus depleting an essential co-factor of the coagulation process. Citrate-iCa molecules are freely filtered and lost in effluent. The rest is metabolized in liver[80]. Each molecule complex releases 3 molecules carbonate and 5 molecules calcium to circulation. The above create several difficulties during CRRT. For achieving anticoagulant effect citrate infusion is adjusted to blood flow in targeting a concentration of 3–6 mmol/l or aiming at a postfilter concentration of iCa of less than 0.35 mmol/l or postfilter ACT 200–250 sec[87]. Since calcium is removed from the circulation, calcium infusion is added in order to maintain normal concentration range. Monitoring about metabolic derangements (hyponatremia, hypercalcemia, hypocalcemia, metabolic acidosis or alkalosis) and appropriate adjustments in citrate and calcium infusions are also essential during RRT. For example, accumulation of citrate due to decreased metabolism can be detected accurately by the symptoms of metabolic acidosis, increasing anion gap, ionized hypocalcemia, and most specifically by an increased total/iCa concentration (a ratio > 2.1 has 89% sensitivity and 100% specificity in predicting citrate concentrations)[88]. In recent years, regional citrate anticoagulation (RCA) in CRRT has become increasingly attractive due to its beneficial low bleeding risk problem. Bai's meta-analysis study demonstrated that regional citrate anticoagulation for CRRT could prolong the filter lifespan and decrease the bleeding risk, compared with heparin anticoagulation[89]. And the KDIGO guideline for AKI recommended RCA rather than heparin in patients who do not have contraindications for citrate. Even in liver failure (LF) patients considering the accumulation of citrate, a recent systematic review and meta-analysis pooled ten observational studies and demonstrated that the RCA might be safe and effective for LF patients underwent CRRT[90].

No anticoagulation, managing contributing factors and other alternatives

No matter how important anticoagulation strategy is, filter life and efficiency is depending on other numerous factors. A recent meta-analysis favors higher blood flow rates and continuous veno-venous hemodiafilatration (CVVHDF) over continuous veno-venous hemofiltation (CVVH)[91]. CRRT has also been performed without anticoagulation with 100–150 ml NaCl 0.9% circuit flush

/ hour[92]. Along with that, technology membranes' progresses over the last years are moving towards limiting anticoagulation needs. Future research might enable use of other intravenous anticoagulant or antiplatelet agents during CRRT (e.g. the adenosine diphosphate receptor inhibitor cangrelor, the thromboxane receptor antagonist terutroban, the phosphodiesterase inhibitor cilostazolor the adenosine reuptake inhibitor dipyridamole).

Conclusion

There are several choices for anticoagulation during CRRT. Yet, the decision to use one over another is a complex task. On one hand, the patient's condition, comorbidities and special characteristics; on the other hand, organizational/ institutional factors, staffing and level of education/experience, type/modes of RRT used, availability of agents chosen and application of a quality assurance program are determinants of the decision about both the anticoagulant and the protocol to be followed.

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Original workt

HOW TO PREDICT NEUROGENIC PULMONARY EDEMA IN ANEURYSMAL SUBARACHNOID HEMORRHAGE? (Neurogenic pulmonary edema in aneurysmal SAH)

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Sumarry

Introduction: *Neurogenic pulmonary edema (NPE) is a clinical syndrome characterized by the acute onset of pulmonary edema after sudden raise of intracranial pressure. NPE is the result of release of catecholamines into the circulation immediately after intracranial hemorrhage. The aim of this study is to investigate a possible correlation between the values of cardiac biomarkers on admission and incidence of NPE in patients with aneurysmal subarachnoid hemorrhage (SAH).* ***Methods:*** *Prospective study includes 262 patients with SAH (162 females). Clinical characteristics, serum cardiac and inflammatory biomarkers were measured on admission and on the day of development of NPE. These data were analysed by tests of statistical significance and binary logistic regression analysis in order to predict the development of NPE.* ***Results:*** *19 patients (7.25%) developed NPE. Statistical analysis revealed that patients who subsequently developed NPE experienced more severe SAH. Cardiac damage was more severe in these patients, as represented by significantly higher number of patients with elevated values of all examined cardiac biomarkers (P from < 0.001 to 0.004). Multivariate regression analysis revealed that elevated troponin I (OR 4.980; 95% CI 1.27–19.49, P = 0.021) and white blood cells count (OR 22.195; 95% CI 3.99–123.50, P < 0.001) were predictors of NPE.* ***Conclusion:*** *Significantly higher number of patients with elevated values of cardiac biomarkers had SAH complicated with NPE. Elevated values of cardiac biomarkers might play an active role in prediction of NPE, although white blood cells count may be involved in the prediction of NPE.*

Key words: *subarachnoid haemorrhage; neurogenic pulmonary edema; cardiac biomarkers ECG changes*

Introduction

Neurogenic pulmonary edema (NPE) is a clinical syndrome characterized by the acute onset of pulmonary edema after a significant central nervous system (CNS) insult[1]. The most common neurological conditions associated with NPE are traumatic brain injury, subarachnoid hemorrhage (SAH), status epilepticus, meningitis or encephalitis, cerebrovascular insults[1,2]. In patients with SAH, reports of NPE incidence range from 2% to 42.9%[1–10]. NPE occurs as a consequence of releasing of catecholamines into the systemic circulation immediately after aneurysmal rupture[2,7,8,10]. Clinically, the likelihood of developing NPE following SAH correlates with increasing age, delayed surgery, vertebral artery origin, and the severity of clinical and radiographic presentation (e.g. Hunt and Hess and Fisher grades)[1,9,11].

Since the catecholamines have direct effect on the myocardium, the aim of this study is to investigate a possible correlation between the value of cardiac biomarkers on admission and incidence of NPE in patients with aneurysmal SAH.

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Material and Methods

From August 2009 to January 2014, the study enrolled 262 consecutive patients admitted to the Neurosurgery Clinic. Inclusion criteria for the study were patients ≥ 18 years of age and the diagnosis of aneurysmal SAH confirmed by cerebral computed tomography (CT) scanning and CT angiography[12]. If the CT angiogram was negative and the suspicion of aneurysm existence was high, the CT angiography was repeated two days later. The inclusion criterion was also the time interval between SAH onset and hospital admission below 96 hours. Chest X-rays were obtained immediately for those suspected of having SAH. Patients with a history of myocardial infarction, cardiomyopathy, or congestive heart failure were excluded from the study.

The study protocol was approved by the Ethics Committee of the School of Medicine, University of Belgrade (No 440/VI-11), and informed consent was obtained from each patient or an appropriate designee. The identity of the enrolled patients was protected. Any clinical procedure was performed in accordance with institutional guidelines. Demographic and clinical data were collected from patient and family interviews and by the review of medical records after enrolment. These data included age, sex, and risk factors for coronary artery disease (CAD). Heart rate (HR) and systolic blood pressure (SBP) on admission were recorded. The severity of neurological injury was graded using each subject's admission Hunt and Hess[13] and Fisher grade[14].

Patients with Hunt and Hess grades I and II were admitted to the neurosurgery ward while those with Hunt and Hess grades III-V to the neurosurgical intensive care unit (NICU).

Clinical management

Every patient was examined daily for the occurrence of NPE. Clinical criteria for NPE included the presence of crackles that suggested fluid in the lungs and presence of frothy pink tracheal fluid. Radiographic criteria for NPE included sharply defined pulmonary markings accompanied by blurring or haziness of the perivascular outlines and loss of demarcation of hilar shadows[8]. All chest X-rays were interpreted by board-certified radiologists blinded to the clinical symptoms of the patient. Patients who fulfilled both clinical and radiographic criteria were diagnosed with NPE. Among the 262 SAH patients, 19 (7.25%) developed NPE. In patients with NPE, arterial blood gas analysis was performed and the type of respiratory support was determined. The time of occurrence of NPE from SAH attack was noted.

The need for inotropic or vasopressor support and time of initiation were documented.

All NICU patients had continuous electrocardiographic (ECG) monitoring and noninvasive blood pressure monitoring (NIBP), as a part of the standard clinical practice. Although central venous catheters were placed routinely, pulmonary artery catheters were not placed[11]. Modified triple-H therapy was initiated in patients with symptomatic vasospasm. The patients were kept normovolemic. In case a patient needed continuous sedation in NICU, Midazolam (0.1–0.2 mg/kg/h) in combination with Remifentanil (0.05–0.2 μg/kg/min) was used. Endotracheal intubation and mechanical ventilation were performed when clinically indicated.

Serum cardiac and inflammatory biomarkers

Each subject was assessed on the day of enrollment. The subjects with NPE were assessed also on the day when NPE was clinically and instrumentally diagnosed.

On each study day, the following biomarkers of cardiac injury and inflammatory biomarkers were measured: creatine phosphokinase (CPK), creatine phosphokinase MB isoenzyme (CPK-MB), creatine phosphokinase MB mass concentration (CPK-MB mass), myoglobin, and cardiac troponin I (TnI), C-reactive protein (CRP), white blood cells (WBC) count, and blood glucose level.

The levels of biomarkers were then dichotomized as elevated for levels exceeding the following values: CPK > 150 IU/L in women and 200 IU/L in men, CPK-MB > 24 IU/L, CPK-MB mass > 5 ng/mL, TnI > 0.04 ng/mL, myoglobin > 110 ng/mL, CRP > 5 mg/L and WBC count > 9.7 x 10^9/L, as well as blood glucose level > 6.1 mmol/L. These cut-offs are adopted according to referent values from our biochemical laboratory.

The time from SAH symptoms onset to measurement of biomarkers was recorded for every patient and it was less than 96 hours.

Neurological assessment

Every patient was neurologically examined in search for signs of hydrocephalus, delayed cerebral ischemia (DCI) or re-rupture. In case of neurological deterioration, a CT scan was performed.

Statistical analysis

262 patients were dichotomized based on the development of NPE. Data were described by frequency and percentage in case of categorical variables, while mean and standard deviation (SD) were run for continuous variables. Data with normal distribution were assessed by Kolmogorov-Smirnov test. For the comparison between NPE+ and NPE– groups, chi-square or Fisher's exact test were used for categorical variables, while the unpaired t-test or Mann-Whitney U test were used for continuous variables where appropriate. Univariate and multivariate logistic regression analysis were used to identify variables predictive of NPE+ outcome. Pearson's correlation between all potential predictors was examined. SPSS 22 (IBM, Chicago, Illinois) was used for statistical analysis and $p < 0.05$ was considered statistically significant.

Results

The study included 262 subjects, of which 7.25% (19 subjects) developed NPE. The total number of examined SAH patients was 368. The number of excluded patients was 106 (28.8%) and the reasons of exclusion are shown on picture 1.

As shown in table 1, the mean age of the 19 study subjects who developed NPE was 52.4 ± 9.5 years. The mean age of 243 subjects who didn't develop NPE was 52.2 ± 11.1 years. There were 84.2% of patients with NPE were women and 60.1% of patients without NPE were women (P = 0.037). The patients who developed NPE had more severe SAH (Hunt and Hess grade > 2), 94.7 vs. 63.0. The mean peak SBP on admission and the heart rate were similar in patients with and without NPE, but history of hypertension (HTA) was more common in patients with NPE (63.2 vs. 36.2, P = 0.02).

Comparison of radiological characteristics (Table 2) revealed similar occurrence of NPE in patients with Fisher grade ≤ 2 and > 2 (63.4 vs. 84.2) (deleted: P = 0.067). However, patients with NPE had higher mean Fisher grade that the group without NPE (3.36 ± 0.76 vs. 2.86 ± 0.84, P = 0.11).

The occurrence of NPE was higher in patients with elevated values of all cardiac biomarkers (Table 3). Elevated WBC count were common in patients who developed NPE (P < 0.001). Among neurological characteristics, none of them were statistically significant in patients with NPE comparing to patients without NPE.

The univariate relationships between the predictor variables and NPE, as determined by logistic regression are shown in Table 3. A Hunt-Hess grade of ≥ 3, female, history of HTA, hydroceph-

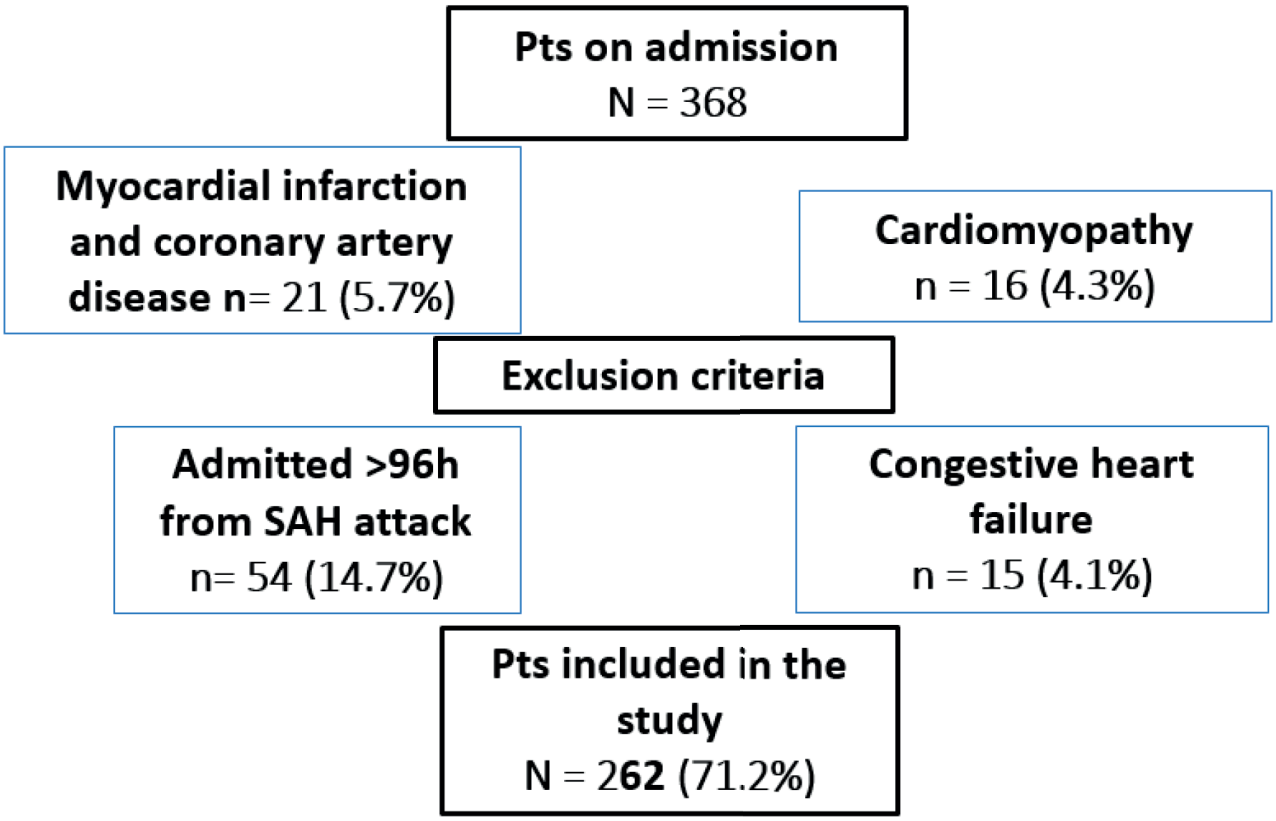

Table 1: Comparison of demographic and clinical variables and risk factors for CAD between SAH patients with and without NPE on admission

	Pts with NPE N = 19	Pts without NPE N = 243	P[b]
Age (mean ± SD), y	52.4 ± 9.5	52.2 ± 11.1	0.943
Female sex, n (%)	16 (84.2)	146 (60.1)	0.037[a]
Clinical characteristics			
Hunt and Hess ≥ 3, n (%)	18 (94.7)	153 (63.0)	0.005[a]
SBP (mean ± SD), mmHg	155 ± 19.4	148 ± 24.7	0.251
HR (mean ± SD), min^{-1}	79.7 ± 18.5	82.3 ± 15.8	0.512
Admission on day of SAH attack, n (%)	13 (68.4)	116 (47.7)	0.082
Risk factors for CAD, n (%)			
History of hypertension	12 (63.2)	88 (36.2)	0.020[a]
History of diabetes	2 (10.5)	44 (18.1)	0.403
History of hyperlipidemia	6 (31.6)	71 (29.2)	0.828
History of smoking	2 (10.5)	60 (24.7)	0.505
Family history of CAD	6 (31.6)	62 (25.5)	0.561

SAH – subarachoid haemorrhage; NPE – neurogenic pulmonary edema; SBP – systolic blood pressure; HR heart rate; CAD – coronary artery disease; SD – standard deviation
[a]Statistically significant
[b]According to chi-square, Student's t-test or Mann-Whitney U test where appropriate

Table 2: Comparison of radiological and neurosurgical variables between SAH patients with and without NPE on admission

	Pts with NPE N = 19	Pts without NPE N =2 43	P[b]
Radiological characteristics			
Fisher > 2, n (%)	16 (84.2)	154 (63.4)	0.067
Anterior circulation aneurysm location, n (%)	17 (89.5)	216 (88.9)	0.938
Multiple aneurysms, n (%)	2 (10.5)	26 (10.7)	0.981
Neurosurgical characteristics			
Secured aneurysm, n (%)	13 (68.4)	201 (82.7)	0.121
Hydrocephalus, n (%)	9 (47.4)	66 (27.2)	0.061
Rerupture, n (%)	5 (26.3)	43 (17.7)	0.350
Seizures, n (%)	5 (26.3)	48 (19.8)	0.493
Secured aneurysm, n (%)	13 (68.4)	201 (82.7)	0.121

SAH – subarachoid haemorrhage; NPE – neurogenic pulmonary edema
[a]Statistically significant
[b]According to chi-square, Student's t-test or Mann-Whitney U test where appropriate (deleted) hart diagram of exclusion process

Table 3: Comparison of biohumoral variables between SAH patients with and without NPE on admission

	Pts with NPE N = 19	Pts without NPE N = 243	p[b]
Biohumoral characteristics			
Troponin I, (mean ± SD), ng/mL, median (IQR)	0.123 ± 0.187 0.064 (0.03–0.12)	0.244 ± 0.88 0.02 (0.01–0.05)	< 0.001[a]
Elevated troponin I, n (%)	14 (73.7)	68 (28.0)	< 0.001[a]
Myoglobin (mean ± SD), ng/mL median (IQR)	220.4 ± 96.4 213 (146–268)	153.6 ± 114.6 124.5 (86–179)	< 0.001[a]
Elevated myoglobin, n (%)	18 (94.7)	151 (63.2)	0.004[a]
CPK (mean ± SD), IU/L, median (IQR)	262.7 ± 115 236 (194–310)	129.5 ± 91.3 98 (69–164)	< 0.001[a]
Elevated CPK, n (%)	17 (89.5)	57 (23.5)	< 0.001[a]
CPK-MB (mean ± SD), IU/L, median (IQR)	22.8 ± 7.8 22 (17–27)	13.9 ± 6.6 12 (9–18)	< 0.001[a]
Elevated CPK-MB, n (%)	7 (36.8)	20 (8.2)	< 0.001[a]
CPK-MB mass (mean ± SD), ng/mL median (IQR)	4.3 ± 1.5 4 (3–5)	2.8 ± 1.4 3 (2–4)	< 0.001[a]
Elevated CPK-MB mass, n (%)	3 (15.8)	9 (3.7)	< 0.001[a]
White blood cells count (mean ± SD), 10^9/L median (IQR)	13.4 ± 2.7 12.7 (11.9–14.8)	9.5 ± 4.3 8.4 (6.4–12.3)	< 0.001[a]
Elevated white blood cells count, n (%)	17 (89.5)	91(37.4)	< 0.001[a]
Blood glucose(mean ± SD), mmol/L, median (IQR)	8.3 ± 1.9 8.3 (6.9–9.6)	8.4 ± 2.8 7.8 (6.3–9.8)	0.740
Elevated blood glucose, n (%)	17 (89.5)	193 (79.4)	0.290
C-reactive protein (mean ± SD), mg/L median (IQR)	10.3 ± 12.4 7.1 (3.6 – 9.6)	5.8 ± 4.7 4.7 (10.3–21.6)	0.094
Elevated C-reactive protein, n (%)	11 (57.9)	110 (45.3)	0.288

SAH – subarachoid haemorrhage; NPE – neurogenic pulmonary edema; SD – standard deviation; IQR – interquartile range; CPK – creatine phosphokinase; CPK-MB – creatine phosphokinase MB isoenzyme; CPK-MB – mass creatine phosphokinase MB mass concentration

[a]Statistically significant

[b]According to chi-square, Student's t-test or Mann-Whitney U test where appropriate

alus, ST-T changes, prolonged QTc interval were all significant predictors of NPE. Elevated values of cardiac biomarkers were significantly more frequent in patients with NPE (P ranged from < 0.001 to 0.017).

Between all the potential predictors examined in univariate logistic regression analysis, we explored Pearson's correlation and found that there is statistically significant correlation between categorical equivalents of cardiac biomarkers (troponin I, myoglobin, CPK, CPK-MB and CPK-MB mass) (r ranged from 0.158 to 0.836, P from < 0.001 to 0.010). Also, we found statistically significant correlation between WBC count, elevated WBC count and CRP (r ranged from 0.316 to 0.816, P < 0.001) and statistically significant correlation between ST-T changes and prolonged QTc (r = 0.611, P < 0.001).

Some of the variables we used are highly correlated, so we didn't include all of them in the multiple regression analysis with intention to avoid a phenomenon of multicollinearity. The consequence of multicollinearity is that coefficient estimates are unstable and difficult to interpret. So

Table 4: Univariate logistic regression analysis to identify variables predictive of NPE associated with SAH

	Univariate[b]		
Predictors	OR	95% CI	P
Age, years	1.002	0.96–1.04	0.943
Female sex	3.540	1.01–12.48	0.049[a]
Hunt and Hess grade ≥ 3	10.992	1.43–84.10	0.021[a]
Anterior circulation aneurysms	0.835	0.18–3.85	0.817
History of HTA	2.785	1.05–7.39	0.040[a]
Hydrocephalus	2.378	0.92–6.17	0.075
Troponin I (elevated)	7.300	2.50–21.24	0.000[a]
Myoglobin (elevated)	11.959	1.57–91.13	0.017[a]
CPK (elevated)	24.672	5.47–111.17	0.000[a]
CPK-MB (elevated)	6.476	2.24–18.68	0.001[a]
CPK-MB mass (elevated)	4.815	1.14–20.19	0.032[a]
White blood cells count (elevated)	15.282	3.42–68.22	0.000[a]
Blood glucose level (elevated)	2.508	0.55–11.31	0.232
C-reactive protein (elevated)	1.645	0.63–4.26	0.306

CI – confidence interval; OR – odds ratio; NPE – neurogenic pulmonary edema; SAH – subarachnoid haemorrhage; HTA – hypertension; CPK – creatine phosphokinase; CPK-MB – creatine phosphokinase MB isoenzyme; CPK-MB – mass creatine phosphokinase MB mass concentration
[a]Statistically significant
[b]Adjusted on sex

Table 5: Multivariate logistic regression analysis to identify variables predictive of NPE associated with SAH

	Multivariate		
Predictors	OR	95% CI	P
Age, years	0.997	0.94–1.06	0.933
Female sex	5.253	1.14–24.16	0.033[a]
Hunt and Hess grade ≥ 3	12.593	1.27–124.79	0.030[a]
History of HTA	3.922	1.07–14.39	0.039[a]
Hydrocephalus	2.028	0.61–6.67	0.244
Troponin I (elevated)	4.862	1.26–18.74	0.022[a]
White blood cells count (elevated)	21.867	4.02–118.75	< 0.001[a]

CI – confidence interval; OR – odds ratio; NPE – neurogenic pulmonary edema; SAH – subarachnoid haemorrhage; HTA – hypertension
[a]Statistically significant

we took one of the variables from each group (elevated troponin I, elevated WBC count and ST-T changes) and put them into the multivariate model together with age, female sex and variables which in univariate model had P < 0.100 (Hunt and Hess grade ≥ 3, history of HTA and hydrocephalus).

After statistical adjustment by multivariate logistic regression (Table 5), elevated TnI (odds ratio (OR) 4.862 per quintile; 95% confidence interval (CI) 1.26–18.74, P = 0.022), elevated WBC count (OR 21.867; 95% CI 4.02–118.75, P < 0.001), being female (OR 5,253; 95% CI 1.14–24.16, P = 0.033), Hunt and Hess of ≥ 3 (OR 12.593; 95% CI 1.27–124.79, P = 0.030), and presence of HTA (OR 3.922; 95% CI 1.07–14.39, P = 0.039), independent risk factors of NPE were established.

Discussion

The incidence of NPE after SAH in our cohort of 262 patients is 7.25%, which is comparable with that reported in the literature (2–42.9%)[1–10]. ECG abnormalities and myocardial enzyme release after SAH are well-known and described[15–17], but the relative contribution of cardiac dysfunction in the pathogenesis of NPE has been unclear. The pathophysiology of NPE is multifactorial. There is evidence that in a subset of patients, neurologic insult leads to direct myocardial injury and the development of NPE. Although the cardiac injury after SAH is more severe in patients who developed NPE, measurement of serum cardiac biomarkers with intention to explore risk factors for occurrence of NPE has rarely been conducted[8,18,19].

In our study, none of the patients on admission had NPE. In study of Inamasu et. al.[18], 11% of the patients were diagnosed with NPE on admission. The lower incidence of NPA in our study could be due to early initiated diuretic therapy (50.8% of all patients) and above all because of early enrollment.

According to the results of demographic comparison (Table 1), NPE was a more common finding in the subgroup of patients with clinically severe hemorrhage (Hunt and Hess grade III-V)[6,8,16]. All patients with NPE presented with radiologically severe bleeding (Fisher grade III, IV), as expected[8]. Although previous studies showed that ruptured posterior circulation was a risk factor for NPE[6,8], the location of aneurysm was not associated with NPE in our study. The lack of statistical difference in our study may also be attributable to the pre-hospital death of those patients.

Higher number of patients with SAH which complicated with NPE had elevated values of cardiac biomarkers levels on admission, and the result is in concordance with the cardiac key role in pathogenesis of NPE[6,10,18,19]. Since cardiac biomarkers were positively correlated, most patients complicated by NPE exhibited a concomitant increase in all of these cardiac biomarkers levels.

Univariate logistic regression analysis revealed that elevated levels of cardiac biomarkers on admission are risk factors for NPE. The elevated values of TnI were significantly more common in patients who would develop NPE which is confirmed by previous studies[8,10,16,18]. The important fact in our study is that none of our patients on admission had NPE. Our clinic is tertiary health center, so very often the SAH therapy has initiated before patient's admission and that can be the cause of our results.

The possibility of prediction of NPE by the elevated WBC is proved in studies where NPE is prevented by attenuating inflammation[20–22]. Finally, multivariate logistic regression analysis verified that elevated TnI and WBC count are risk factors for NPE.

There are several limitations in our study. First, we had no possibility to use transthoracic echocardiography (TTE) examination of the heart structure and function. This could enable to assess role of the heart dysfunction in pathophysiology of NPE[23]. Zaroff et al.[10] found that the great majority of patients with NPE were complicated by concomitant wall motion abnormality. In another study, Inamasu et al.[6] also found that 88% of the patients with NPE had also Takotsubo cardiomyopathy. Tung et al. revealed that 23% of patients with regional wall motion abnormalities had pulmonary edema[24]. Secondly, a different time from SAH onset to admission at the hospital could also have influenced the results. Third, we had only one measurement for the examined variables which are measured within 96 hours of SAH onset. The results of this study although interesting should be viewed cautiously because of the low number of patients identified with NPE.

Despite these limitations, this study is unique because cardiac biomarkers on admission in prediction of SAH-induced NPE were evaluated for the first time, and we believe that it might provide a new insight into the pathogenesis, however further evaluation is needed.

Conclusions

The elevated values of cardiac biomarkers on admission appear to play an active role as risk factors for NPE. Although we didn't use TTE examination in our study, we recommend it to confirm or exclude global or regional left ventricular systolic dysfunction and to ensure that therapeutic decisions are based on the cardiac status of each patient.

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Revijalni članak

DOPLER DIJAGNOSTIKA VASKULARNOG SISTEMA

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Sažetak

Vaskularne bolesti su u Srbiji vodeći uzrok smrti i invaliditeta kod ljudi starijih od 50 godina. Ultrasonografski pregled krvnih sudova je brz, za bolesnika bezbolan, bezopasan i komforan, a za zdravstveni sistem zemlje, odnosno pacijenta, ekonomski isplativ i precizan. Danas je ova dijagnostička metoda „zlatni standard" u primarnoj dijagnostici, skriningu i praćenju vaskularnih bolesti. Kolor dupleks (colour duplex) široko je rasprostranjena, neinvazivna procedura visoke senzitivnosti, koja čini kombinaciju pulsnog doplera i prikaza tkiva u realnom vremenu (real time B-mode). Ona omogućava da se na ekranu, u realnom vremenu, prati protok krvi kodiran bojom, unutar dvodimenzionalnog B-moda. U vaskularnoj ultrasonografiji se koriste linearne i konveksne sonde. Konveksna i sektorska sonda najčešće se koriste za prikaz duboko postavljenih struktura u abdomenu, maloj karlici ili grudnom košu. One rade na frekvenciji 2,5–5 MHz. Linearne sonde rade na znatno višim frekvencijama (7–13 MHz). One se koriste za prikaz površnije postavljenih struktura. Ultrasonografija u dijagnostici oboljenja krvnih sudova podrazumeva primenu različitih modaliteta, a sa ciljem procene morfoloških karakteristika krvnog suda i protoka kroz njega. Savremeni ultrazvučni sistemi podrazumevaju primenu B-moda i pulsnog doplera objedinjenih kao duplex scan. Kvalitativna procena arterijskog protoka je moguća analizom akustičkog talasa koji prezentuje arterijski protok. U slučaju grafičkog zapisa na ekranu ili papiru, moguća je analiza spektralnih arterijskih kriva protoka.

***Ključne reči**: vaskularna ultrasonografija; dopler*

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Review article

VASCULAR SYSTEM DOPPLER DIAGNOSTIC

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Sumarry

SVascular diseases are the leading cause of death in Serbia and disability in people over 50 years of age. Ultrasonography examination is quick, painless, safe and comfortable for patients, and for the public health care system inexpensive and accurate. Currently, this diagnostic method represents a "gold standard" in the primary diagnosis, screening and monitoring of vascular diseases. Color duplex is a widely used, non-invasive and highly sensitive procedure, which is a combination of pulse Doppler and real time B-mode. It enables an on-screen, real time observation of the blood flow, color coded within two-dimensional B-mode. In vascular ultrasound, both linear and convex probes are used. Convex and sector probes are used to show deep set structures in the abdomen, pelvis or chest. They operate at frequencies between 2.5 and 5 MHz. The linear probes operate at much higher frequencies (7 to 13 MHz). They are used for imaging of more superficial structures. Ultrasonography in the diagnosis of blood vessel diseases involves the application of modalities in order to assess morphologic characteristics of a blood vessel and a flow through it. Ultrasound systems include the B-mode and pulsed Doppler integrated as Duplex scan. Qualitative assessment of blood flow is possible by analyzing the acoustic waves that presents the arterial flow. Graphic record on the screen or paper enable analyzes of spectral arterial flow curves.

***Key words**: vascular ultrasonography; Doppler*

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Uvod

Dijagnostika oboljenja krvnih sudova temelji se na primeni Doplerovog efekta. Urich je 1947. godine prvi obavio merenje brzine prolaska ultrazvuč nih talasa kroz tkivo sisara. Razvojem vaskularne hirurgije, tehnološki napreduje i neinvazivna dijagnostika. Od sredine osamdesetih godina 20. veka počinje upotreba kolor dupleks (*Color Duplex* – CD) ultrasonografije[1,2,3]. U dopler dijagnostici se primenjuju dve vrste ultrazvučnih talasa: Dopler kontinuira nih ultrazvučnih talasa (*CW Doppler*) i Dopler pulsnih ultrazvučnih talasa (*PW Doppler*).

CW doppler

Kontinuiranim doplerom indirektno se analizira hemodinamska reperkusija patoloških promena peri fernih krvnih sudova. Pri ispitivanju ovim načinom, ispituje se celi promer krvnog suda i dopler ultrazvučni signal sadrži informacije o svim brzinama profila toka strujanja[2].

Ankle brachial index

Ankle brachial index – ABI (poznat kao *ankle arm pressure index*, *ankle systolic pressure index*, pedobrahijalni indeks) predstavlja odnos pritiska na nivou nožnog zgloba i brahijalnog pritiska[4]. Pritisak iznad članka se menja sa centralnim aortnim pritiskom i to je poželjno poređenje pri svakom merenju tog pritiska. Meri se na klasičan način, pomoću manžetne koja se naduvava do suprasistolnih vrednosti, a kao detektor pojave protoka služi dopler ultrazvučni instrument (sonda) frekvencije od 8 MHz[4].

Ankle brachial index je najjednostavniji pokazatelj prisutnosti i stepena obliterirajućih pro mena arterija donjih ekstremiteta. Ovim merenjem se uspešno ocenjuje stepen progresije bolesti i uspešnost lečenja[4]. Poteškoće pri određivanju vrednosti sistolnih pritisaka i njihova interpretacija mogu da se jave kod slabog signala, multisegmentne bolesti i nekompresibilnosti arterije. U odsustvu proksimalnih arterijskih bolesti, ABI je uvek veći od 1, sa sred njim variranjem od 0,10 (Tabela 1)[4].

Tabela 1: Stepen arterijske insuficijencije u odnosu na vrednosti *Ankle brachial index* (ABI)

Normalne vrednosti	1,00 ± 0,10
Laka arterijska insuficijencija	0,75–0,90
Funkcionalna nesposobnost	0,50–0,75
Teška arterijska insuficijencija (indikovana angiografija)	0,35–0,50
Bol u miru	0,25–0,35
Preteća gangrena	< 0,25

Segmentni sistolni pritisak (*Segmental Blood Pressures* – SBP)

ABI ne može da odredi lokaciju proksimalne lezije niti da ukaže na multi segmentne promene. Ove informacije mogu se dobiti merenjem sistolnog pritiska na različitom nivou ekstremiteta kod pacijenata sa abnormalnim pritiskom iznad članka[4]. U ovoj proceduri se primenjuju četiri manžetne od 41 cm do 83 cm dužine i 11 cm širine za svaku nogu. Manžetne se postavljaju u nivou butine, iznad kolena, ispod kolena i u nivou članka. Sistolni pritisak se određuje dopler ultrazvukom, postavljanjem sonde preko *arterije tibialis posterior* ili *arterije tibialis anterior*[5].

Sistolni pritisak u nivou butine, meren ovom metodom, normalno nadvisuje brahijalni pritisak za 30–40 mmHg. Indeks je veći od 1,2. Ukoliko se kreće između 0,8–1,2, pobuđuje sumnju da se radi o aortoilijačnoj stenozi, dok indeks manji od 0,8 odgovara kompletnoj okluziji arterije ilijake[6].

Razlika sistolnog pritiska između dva susedna nivoa na nozi ili istih nivoa obe noge treba da bude manja od 20 mmHg kod zdravih pojedinaca. Ukoliko je razlika veća od 20 mmHg, ona ukazuje na prisutnu okluzivnu bolest odgovarajućeg segmenta[4,5,6].

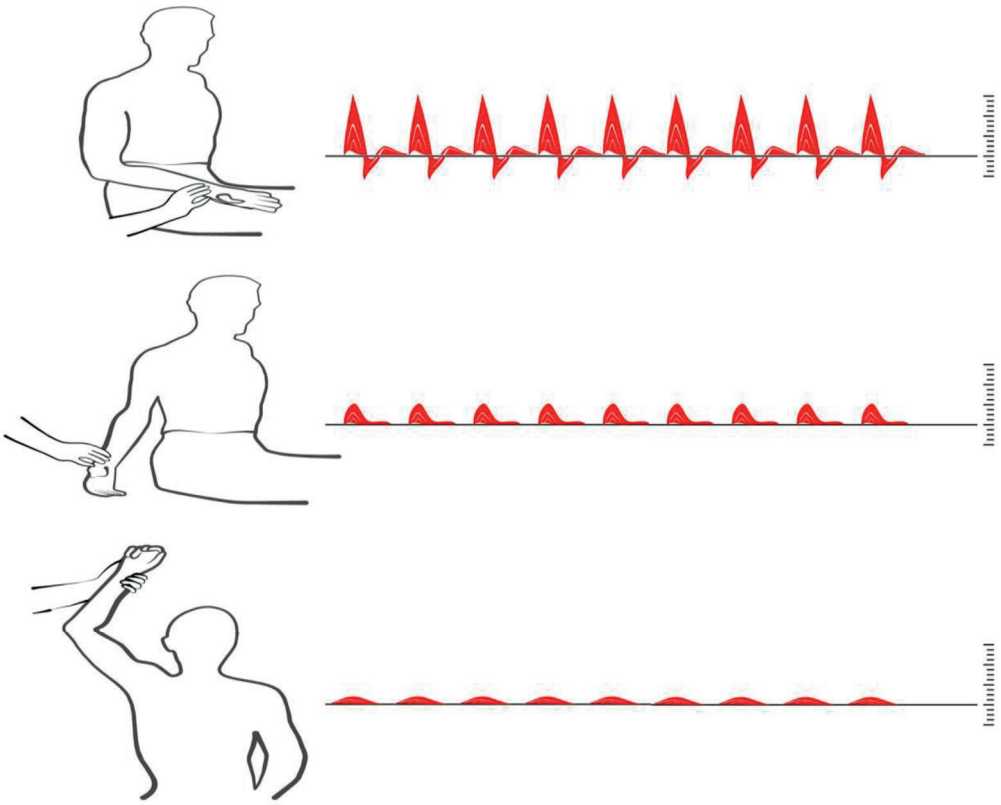
Segmentni sistolni pritisci gornjih ekstremiteta

Ateroskleroza ređe zahvata gornje ekstremitete, a opstruktivne lezije su uglavnom upalne etiologije (arteritisi)[4]. Najčešća patologija su vazospastični poremećaji i sindrom gornje torakalne aperture[5].

Na rukama se određuju sistolni pritisci na nadlaktici, podlaktici, zatim pri elevaciji i Adso novom

manevru. Merenje se izvodi uz pomoć dopler ultrazvuka, sondom frekvencije 8–10 MHz. Razlika sistolnog pritiska dva susedna nivoa na ruci ili istih nivoa obe ruke treba da bude manja od 10 mmHg (< 10%). Razlika veća od 10 mmHg (> 10%) ukazuje na prisustvo stenoze na odgovarajućem nivou. Takođe, vrednosti se porede pri elevaciji i Adsonovom manevru (Slika 1)[4,5,6].

ishemija i vazodilatacija distalno od manžetne. Promene pritiska iznad članka nakon otpuštanja manžetne su slične onim posmatranim tokom testa opterećenja. Mada normalno ekstremiteti ne pokazuju pad *ankle systolic pressure* nakon testa opterećenja, kratkotrajan pad se dešava tokom testa reaktivne hiperemije. Ovaj pad *ankle pressure* je u opsegu od 17–34%[5,6,7].



Slika 1: Šema izvođenja testova pri sumnji na arterijski *Thoracic Outlet Syndrome* (*TOS*). A. Registrovanje trofazičnog pulsnog talasa nad radijalnom arterijiom u normalnom položaju; B. Izmenjena kriva protoka bifazičnog pulsnog talasa pri Adsonovom manevru; C. Monofazičan talas protoka radijalne arterije u položaju elevacije zbog kompresije vratnog rebra na potključnu arteriju.

Test reaktivne hiperemije

Reaktivna hiperemija je alternativan metod opterećenja periferne cirkulacije, zamena za test opterećenja. Test je imitacija odgovora na opterećenje vežbanjem. Primenjuje se kod pacijenata sa neodgovarajućim kardiološkim statusom, teškim plu ćnim oboljenjem, sa ishemičnom ulceracijom na nozi, kod pacijenata koji ne smeju ili ne mogu na pokretnu traku (neuromuskuloskeletne bolesti, amputirani donji ekstremitet)[6].

Procedura izvođenja samog testa zasniva se na naduvavanju manžetne u nivou butine suprasistolnim pritiskom, čime se nakon 3–5 minuta stvara

Tumačenje testa podrazumeva da je kod pacijenata sa promenjenim arterijama odgovor na reaktivnu hiperemiju nagla še niji. Pacijenti sa jednosegmentnom opstrukcijom imaju pad pritiska do 50%, a pacijenti sa višesegmentnom opstrukcijom imaju pad veći od 50%[5,6,7].

Ograničenje testa je loša tolerabilnost same procedure kod mnogih pacijenata zbog bola uzrokovanog stezanjem manžetne. Iako je test pogodan za otkrivanje „skrivenih" okluzivnih bolesti, diferencijacija pravih vaskularnih klaudikacija od pseudoklaudikacija nije dobra. Test opterećenja je pogodniji test, jer stvara fiziološko opterećenje i reprodukciju pacijentovih simptoma[4,5,6,7].

Test opterećenja (*treadmill exercise test*)

Test opterećenja na pokretnoj traci je najbolji pokazatelj stepena arterijske insufici jencije, arterijske kolateralizacije i objektivno merilo toka bolesti i rezultata lečenja[6]. Test je koristan zato što simultana aktivnost proizvodi pacijentove simptome i određuje stepen nesposobnosti[4]. On dozvoljava procenu porekla tegoba, funkcionalne sposobnosti i značenje stenoze u multisegmentnoj bolesti.

Test opterećenja je važan za jasnu procenu pacijenata koji imaju prave klaudi ka cije od onih koji imaju pseudoklaudikacije, kao što su pacijenti sa spinalnom stenozom, lumbalnom ishialgijom i drugim nevaskularnim uzrocima. Test opterećenja je određen i pacijentovom snagom, motivacijom i tolerancijom bola[5].

Indikacije za izvođenje testa opterećenja su:

1. pacijenti koji se žale na bol u nogama tokom hoda
2. niže vrednosti ABI (naročito 0,50–0,90)
3. kontrola stepena progresije bolesti
4. kontrola postoperativnih rezultata.

Kontraindikacije za izvođenje testa opterećenja su iste kao kod testa opterećenja srca, ishemijske ulceracije na nozi, amputi rani ekstremiteti[6]. Tokom testa se analizira vreme hodanja bez tegoba, maksimalna klaudikaciona distanca, karakter i lokalizacija bola, promena sistolnog pritiska iznad članka, vreme oporavka i vraćanja na nivo pre opterećenja. Normalan odgovor na napor je neznatno povećanje i bez promene vrednosti sistolnog pritiska iznad članka u odnosu na vrednosti pre opterećenja[4,5,6,7].

PW dopler

Kolor dupleks (*Color Duplex* – CD) ultrasonografija predstavlja široko rasprostranjenu neinvazivnu proceduru visoke senzitivnosti[7]. Kombinacija je pulsnog doplera (PW) i prikaza tkiva u realnom vremenu (*real time B-mode*). Omogućava da na ekranu u momentu događanja pratimo protok krvi unutar dvodimenzionalne B-slike kodirane bojom. B-prikaz (*B-mode*, *brightness modulation*) predstavlja dvodimenzionalni prikaz, način registracije, gde svetle tačke označavaju mesto s kojeg se vratio odjek, a mesta gde nema odjeka su bez zapisa. Upotreba tzv. sive skale (*gray scale*) omogućava gradaciju intenziteta svetline između crnog i belog i označava prikaz kod kojeg je svetlina tačke na ekranu proporcionalna intenzitetu primljenog odjeka. U CD ultrasonografiji dobijene dopler informacije su prikazane u obliku grafičkog prikaza spektra pulsnih talasa i boje protoka krvi u krvnom sudu. Koristi se dopler pulsnih talasa, koji za razliku od CW doplera ima mogućnost promene frekvencije i dubine pulsnog talasa. U praktičnom smislu, pulsni talas može da se upravlja u određena tkiva, konkretno u lumen krvnog suda. Analiza spektra pulsnih talasa je ista kao kod CW doplera. Kolor dopler informacije prikazuju ukupan protok u krvnom sudu. Smer je kodiran crveno–plavo. Crveno predstavlja anterogradni smer (u smeru strujanja krvi), a plavo inverzan – povratan tok. Svetle nijanse svake boje predstavljaju veće frekvencije, a maksimalna brzina je prikazana belom bojom[7].

U vaskularnoj ultrasonogafiji se koriste linearne i konveksne sonde. Konveksne i sektorske sonde se najčešće koriste za prikaz duboko postavljenih struktura u abdomenu, maloj karlici ili grudnom košu. One rade na frekvenciji 2,5–5 MHz. Za razliku od njih, linearne sonde rade na znatno višim frekvencijama (7–13 MHz). One se koriste za prikaz površnije postavljenih struktura. Što znači da sonde koje rade na niskim frekvencijama dozvoljavaju prikaz duboko lociranih struktura i patoloških promena sa manjim brojem detalja, dok se korišćenjem sondi koje rade na visokim frekvencijama dobija kvalitetan prikaz, ali samo površno postavljenih struktura[7].

Spektralna analiza

Reč *spectrum* potiče iz latinskog jezika i znači slika. Dopler spektar je u stvari slika stvorena kretanjem krvi. Spektar pokazuje izmešane dopler frekvencije prisutne u ehu suda u svakom trenutku vremena. Normalan pulsni talas je trofazičan.

Sistolna komponenta odgovara sistoli srca. Rana dijastolna komponenta predstavlja kratkotrajnu promenu smera krvi zbog pada pritiska u levoj komori, a kasna dijastolna komponenta je anterogradnog smera. Kvalitativna i kvantitativna analiza dopler spektra označava analizu oblika krivulje, brzinu protoka, kao i određivanje indeksa rezistencije i pulsatilnog indeksa.

Krive protoka nad visceralnim arterijama (renalnim arterijama, mezenteričnim arterijama pre obroka, unutrašnjim karotidnim arterijama) najčešće imaju izgled monofaznih kriva, s obzirom na nisku vaskularnu rezistenciju u distalnim segmentima.

Pulsativni indeks (PI) predstavlja meru oscilatorne energije protoka – brzine talasa[7]. Stenoza suda dovodi do redukcije PI distalno od mesta stenoze.

$$\text{Pulsativni indeks } \mathbf{(PI)} = \frac{\text{A - B}}{\text{srednja frekvencija}}$$

Indeks rezistencije (RI) koristi se kao indikator otpora cirkulacije iza tačke merenja[7]. Stenoza dovodi do redukcije protoka krvi i povećanja otpora. Visoki indeks rezistencije može da bude i znak sniženja protoka u kapilarnom sistemu.

$$\text{Indeks rezistencije } \mathbf{(RI)} = \frac{\text{A - B}}{\text{A}}$$

Tabela 2: Kriterijum za klasifikaciju periferne lezije arterija

Klasifikacija	**Karakteristike**
Normalno	Trofazičan pulsni talas
1–19%	Trofazičan talas sa minimalnim spektralnim proširenjem
20–49%	Trofazičan talas povećanih sistolnih brzina, jasnog spektralnog širenja

Morfološki parametri koje pratimo su: kalibar arterijskog suda, zidovi suda, postojanje parijetalnih depozita, karakter depozita (tromb ili ateromatozni plak), stepen stenoze, kao i postojanje ekstraluminalnih masa koje kompromituju protok kroz ispitivani sud[4,7]. Hemodinamski parametri su vršne sistolne brzine, kao i gradijent brzine, koji predstavlja odnos vršne sistolne brzine na mestu stenoze i prestenotično[4,5,6,7].

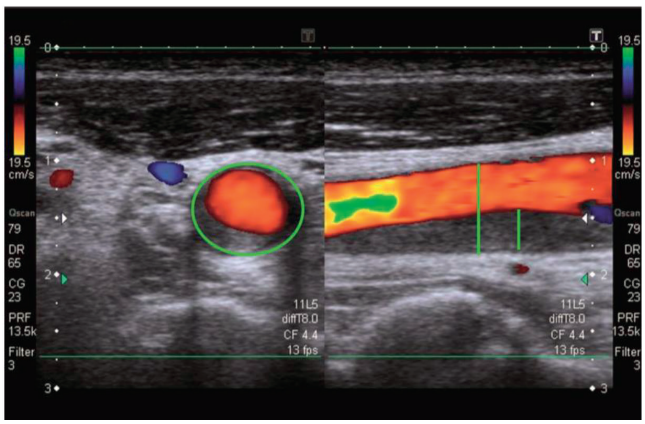
Artefakti ultrasonografije

Artefakti su formacije koje ne postoje i koje imitiraju normalne ili patološke strukture. Tokom ultrasonografije karotidnih arterija nastaju zbog neispravnosti opreme, neadekvatnog podešavanja parametra pregleda, neispravne obrade slike i uticaja posmatrane sredine[7].

Ultrazvučni pregled karotidnih arterija

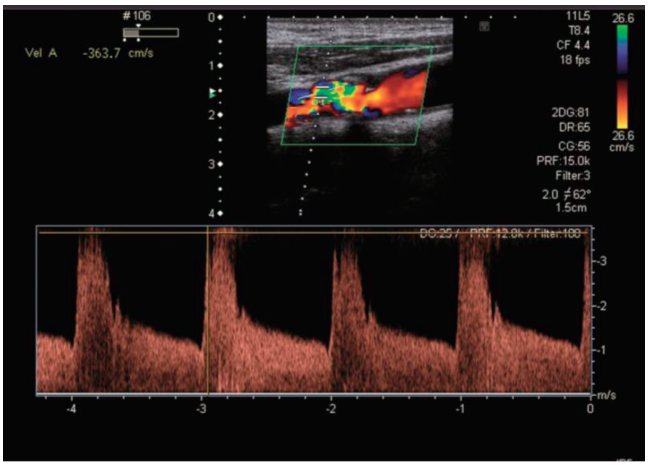
Značaj pregleda karotidnih arterija leži u činjenici da se centralni nervni sistem snabdeva krvlju preko četiri arterijska suda, dve karotidne i dve vertebralne arterije. Ultrazvučni pregled karotidnog sliva podrazumeva pregled zajedničkih karotidnih arterija, kao i ekstrakranijalnih segmenata spoljašnje i unutrašnje karotidne arterije. Pregled obavljamo linearnom sondom frekvencije 7–10 MHz.

Pouzdana detekcija karotidne stenoze ili okluzije pomoću kolor dupleks ultrasonografije uglavnom je moguća kombinacijom B-moda i *color flow* prikazom[7,8,9]. B-modom se definišu spoljne granice krvnog suda i redukcija lumena, dok se kolor imidžingom pokazuje uzorak protoka. Dopler spektralna analiza služi da potvrdi imidžing nalaz i neophodna je za kvantifikaciju. Stepen karotidne stenoze može biti procenjen merenjem dijametra ili area rezidualnog lumena i dijametra ili area orginalnog lumena (Slika 2).



Slika 2: Kolor dopler prikaz poprečnog preseka ACI (area stenoze i dijametar stenoze)

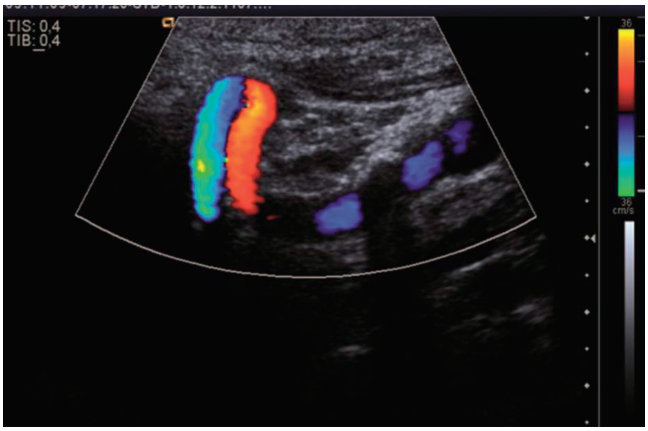
Tačnost merenja stenoze karotidnih arterija zavisi od dobrog kvaliteta slike i postizanja pravog poprečnog preseka krvnog suda. Kvalitativan poprečan presek ne može uvek da se dobije, ako su krvni sudovi tortuozni ili su sa kalcifikovanim plakovima[7,9]. U takvim slučajevima stepen stenoze mora da se proceni na osnovu dopler spektralne analize (Slika 3).



Slika 3: Visokostepena stenoza ACI sa porastom brzina > 300 cm/s, enddijastolne brzine 120 cm/s. U nivou stenoze istovremeno se registruje anterogradni i reverzni protok sa spektralnim proširenjem.

Vertebralne arterije neizostavno pregledamo u istom aktu kada i karotidne arterije. Pacijent je u istom položaju kao za pregled karotidnih arterija i pregled se obavlja istim sondama. Takođe, treba pomenuti elongacije i tortuoznost karotidnih arterija.

Tortuoznost je izduženost krvnog suda u obliku slova S ili C. Za razliku od tortuozno izmenjene arterije, kinking je presavijenost krvnog suda pod oštrim uglom. Koiling je elongiranost krvnog suda u obliku petlje (Slika 4).



Slika 4: Kinking unutrašnje karotidne arterije, ugao manji od 30°

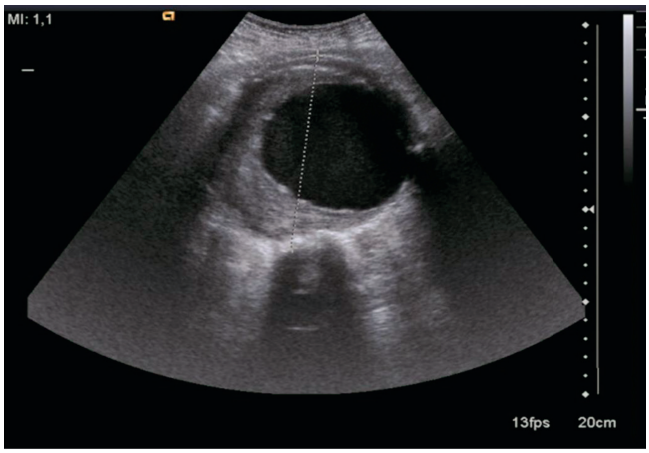
Kod pregleda vertebralnih arterija problem nam predstavljaju koštane strukture, zbog specifične anatomije. Po ulasku u transverzalne vertebralne otvore, od vertebralnih arterija vidimo samo kraće segmente.

Kao i kod karotidnih arterija, određujemo dijametar vertebralne arterije (oko 4 mm), utvrđujemo postojanje depozita, obeležavamo smer kretanja krvi (stenoza ili okluzija istostrane potključne arterije dovodi do sindroma krađe krvi iz vertebralne arterije i reverznog protoka krvi kroz ispitivanu vertebralnu arteriju), merimo brzinu protoka krvi (vršna sistolna brzina ne sme biti manja od l0 cm/sec)[7,8,9].

Ultrazvučno ispitivanje abdominalne aorte

Abdominalna aorta, kao dominantni arterijski sud u abdomenu, sonografski je jasno definisanih zidova, postavljena lako ulevo od središne linije. Maksimalni promer iznosi oko 20 mm, dok su ilijačne arterije promera oko 10 mm.

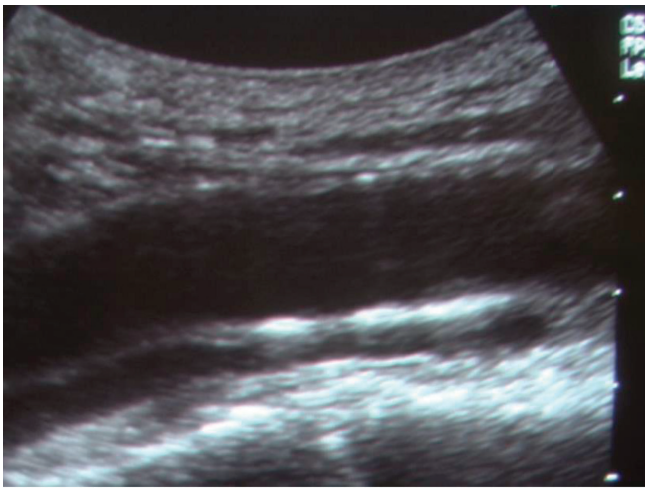
Otkrivanje aneurizmi abdominalne aorte je najčešći zadatak za dijagnostičara. Smatra se da je arterija aneurizmatski izmenjena ukoliko joj je dijametar uvećan za 1,5 do 2 puta u odnosu na uobičajeni. Utvrđuje se maksimalni promer aneurizme, oblik, longitudinalna ekstenzija i postojanje parijetalnog tromba (Slika 5).



Slika 5: Infrarenalna aneurizma, dijametra 104 mm, sa cirkumferentnim trombnim masama koje ispunjavaju 1/3 lumena

Sa hirurškog aspekta je izuzetno važno određivanje nivoa od kog se aneurizma pruža, te je obaveza svakog dijagnostičara da izmeri tačnu dužinu aortnog segmenta od ishodišta renalnih arterija do početka aneurizme (imajući u vidu da je najveći broj aneurizmi infrarenalno lokalizovan).

Disekcija abdominalne aorte je prodor krvi kroz oštećenje intime u mediju arterije. Obično počinje u torakalnom delu aorte, te se pruža prema abdominalnom delu aorte[10]. Sonografski se uočava kao dvostruki lumen arterije (tanka, hiperehogena, membrana deli lumen na dva odeljka) od kojih „lažni" može da bude aktivan, tj. protočan ili tromboziran. Disekcija može, ali ne mora da bude udružena sa postojanjem aneurizme (Slika 6)[7,10].



Slika 6: Disekantna aneurizma, longitudinalni presek

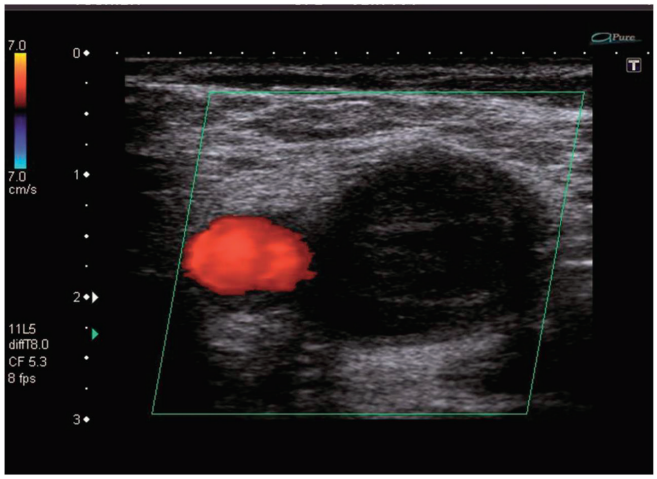
Ultrazvučno ispitivanje vena

Upotreba dupleks ultrasonografije u dijagnostici venskih oboljenja je postala rutinska metoda u svim vaskularnim ambulantama. Ona ima nekoliko važnih karakteristika: (1) odličnu prostornu rezoluciju, sadržanu u opsegu frekvencije od 5 do 10 MHz; (2) odličnu rezoluciju sive skale (dinamičan opseg); (3) pulsni dopler koji je dovoljno osetljiv da detektuje male brzine protoka prisutne u manjim venama. Problem predstavljaju gasovi, kost i veće količine tečnosti koje oslabljuju penetraciju dopler talasa.

U slučaju normalnog nalaza, slika vene na kolor dupleksu ima sledeće karakteristike:

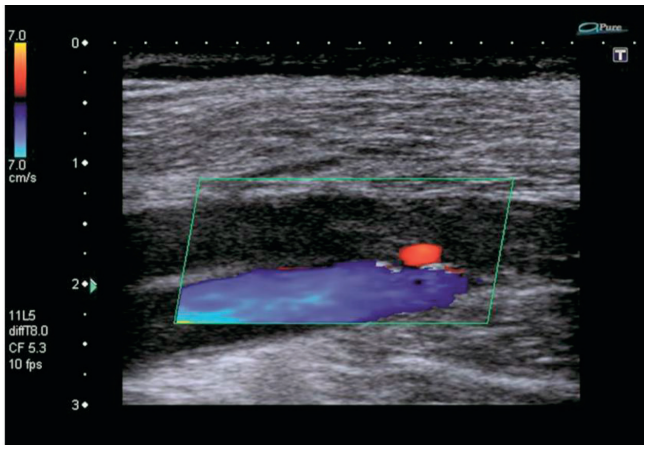
1. *Anehogenost* – lumen normalne vene je anehogen, unutrašnja površina venskog zida je glatka. U slučaju zadebljanja zida, možemo da govorimo o poremećaju. Valvule mogu povremeno da se vide kada je kvalitet slike odličan.
2. *Kompresibilnost* – venski lumen može da bude obliterisan i malim spoljašnjim pritiskom.
3. *Veličina vena u odnosu na arterije* – glavne vene ruke i natkolenice su umereno većeg dijametra od odgovarajućih arterija. Ako su vene bitno veće od arterija, više od dva puta, venska tromboza je suspektna. Vene mogu da budu povećane zbog kongestivne slabosti srca.

Dopler karakteristike normalnih vena imaju pet važnih obeležja: spontanost, fazičnost, Valsalva odgovor, augmentacija na distalnu kompresiju i usmerenost protoka u pravcu srca. Akutna tromboza, koja se manifestuje kao inicijalna tromboza, najčešće nastaje u sinusima solealnog mišića. Kod 80% pacijenata ne dolazi do propagacije ili embolizacije, već dolazi do spontane lize tromba ili rekanalizacije. U 5% slučajeva potkolena flebotromboza može da dovede do embolizacije. Akutna venska tromboza se odnosi na period 1–2 nedelje nakon početka procesa. To je period kada najčešće dolazi do embolizacije. Kolor dupleks ultrasonografski se uočavaju hipoehogene trombne mase, gubitak kompresibilnosti i venska distenzija (Slika 7).



Slika 7: Akutna tromboza površne femoralne vene. Dijametar površne femoralne vene je dva puta veći od dijametra površne femoralne arterije.

Uopšteno posmatrano, termin „hronična venska tromboza" je pogrešan, pravilnije je reći hronične sekvele venske tromboze. Vremenom dolazi do adherencije tromba za venski zid i njegove organizacije. Odlikuje se hiperehogenim trombnim masama i dijametrom vene koji odgovara normalnom nalazu (Slika 8).



Slika 8: Organizovana tromboza površne femoralne vene sa hiperehogenim trombnim masama

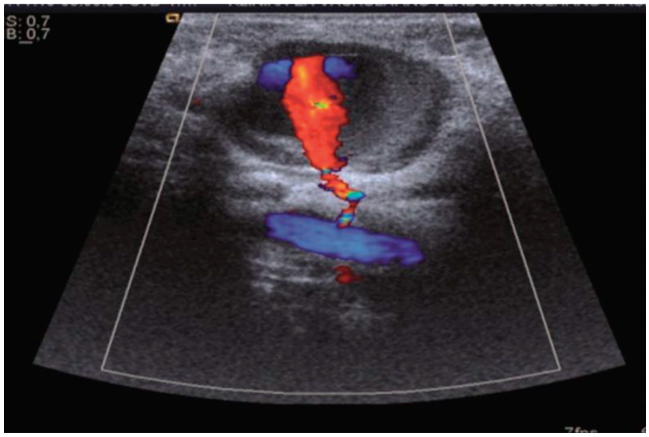
Tromboza vena ruku retko nastaje i najčešće je posledica preteranog fizičkog napora. Tromboflebitis natkolenog dela *vene safene magne* može da dovede do embolizacije kod 10% hospitalizovanih pacijenata. Klinički nalaz je karakterističan – trakasto zapaljenje kože sa okolnim eritemom i edemom, a ultrazvučni nalaz često pokazuje proksimalniju propagaciju trombotičkog procesa[11,12,13].

Nekoliko različitih stanja mogu da imitiraju znake i simptome duboke venske tromboze: kongestivna srčana insuficijencija, apsces, adenopatija, tumor mekih tkiva, Bejkerova cista (Baker's cyst) i limfedem. Senzitivnost i specifičnost CD ultrasonografije u dijagnostici femoropoplitealnih flebotromboza je 90–100%, a flebotromboza vena potkolenice 60–90%[13]. Kod 25–30% pacijenata sa angiografski dokazanom plućnom embolijom tromboza vena ekstremiteta je odsutna[13]. Ultrasonografski skrining visokorizičnih pacijenata se ne radi, već se vrši pregled pacijenata koji imaju simptome tromboze dubokih vena ili plućne embolije[7,11,12,13].

Neinvazivno ispitivanje povreda krvnih sudova

Ultrazvučna dijagnostika ima značajnu ulogu u otkrivanja bolesti i u praćenju operisanih bolesnika. Nakon hirurške rekonstrukcije krvnog suda, potrebno je isključiti postojanje komplikacija kao što su krvavljenje i formiranje hematoma, infekcija i stvaranje perigraftnih kolekcija, pseudoaneurizmi na anastomozama, kao i stenoza i okluzija grafta.

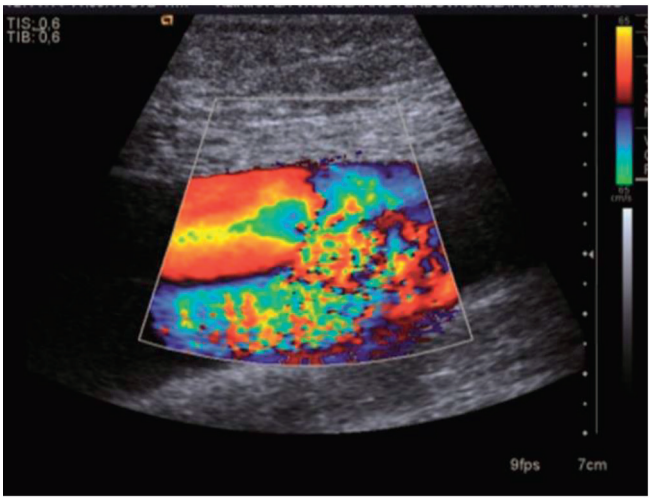
Na postojanje pseudoaneurizme potrebno je posumnjati u svim slučajevima kada se nakon angiografske procedure u nivou punkcije javi otok praćen jakim bolom. Osim bolne osetljivosti na palpaciju, auskultacija može da ukaže na postojanje šuma. Metoda izbora u dijagnostici pseudoaneurizmi perifernih arterija je *color duplex scan*[7,12]. Njegova senzitivnost i specifičnost u dijagnostici pseudoaneurizmi femoralne arterije je 95 do 98%[7] (Slika 9).



Slika 9: *Color duplex scan* pseudoaneurizme zajedničke femoralne arterije nakon PCI procedure

Razvoj ultrazvučne dijagnostike od dopler spektralne analize kontinuiranih talasa do dupleks ultrasonografije i kolor dupleks ultrasonografije je omogućio utvrđivanje postojanja arteriovenskih (AV) fistula ekstremiteta, kao i većine visceralnih grana. Ova metoda ne može pouzdano da isključi postojanje AV fistule ukoliko su njene hemodinamske osobine od manjeg značaja[2,7,12]. Zadatak ultrasonografije je da odredi morfološke osobine AV fistula (mesto, veličinu, strukturne promene arterije i vene spojene fistuloznim kanalom, postojanje hematoma i drugih promena okolnog tkiva) i hemodinamske osobine (protok kroz AV fistulu, arteriju i venu proksimalno i distalno od mesta fistule, postojanje venske i arterijske insuficijencije).

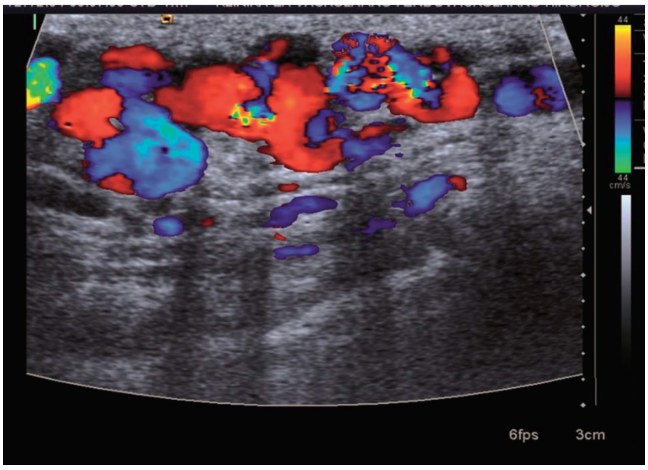
Mesto komunikacije se kolor dopler tehnikom prikazuje u vidu višebojnih blještećih polja, od nijansi narandžaste do bele boje, koja se šire u venu neposredno i proksimalno od komunikacije, kao i prekomunikaciono u arteriji (Slika 10)[2,7,12,14,15].



Slika 10: *Color duplex scan* nalaz arteriovenske fistule femoralnih krvnih sudova

Kongenitalne vaskularne malformacije

Kongenitalne vaskularne malformacije su heterogena grupa retkih displazija koja zahvata arterijski, kapilarni, venski ili limfatički sistem. One su pristutne na rođenju, mogu da se povećaju i da se nikad spontano ne regresiraju[15]. U poslednjih nekoliko decenija se dosta saznalo o histopatologiji, etiologiji i tretmanu vaskularnih anomalija, što je dovelo do promena u klasifikaciji i terminologiji koja se koristi pri opisu ovih patoloških stanja. Često se koriste nazivi latinskog porekla *hemangioma simplex*, *angioma telangiectaticum*, *hemangioma cavernosum*. Mnoge vaskularne anomalije mogu da se dijagnostikuju fizikalnim pregledom i istorijom bolesti. Međutim, ultrasonografija i magnetna rezonanca su najvažniji imidžing modaliteti (Slika 11).



Slika 11: *Color duplex scan nalaz hemangioma*

Arteriovenske malformacije i arteriovenske fistule su tipično kongenitalne i stečene malformacije, koje se karakterišu mnoštvom arterijskih i venskih kanala, visokog protoka, bez postojanja značajne solidne formacije[1,2,7,12,15].

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