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TRANEKSAMIČNA KISELINA U TRAUMOM INDUKOVANOJ KOAGULOPATIJI

Summary: Trauma is still the leading cause of death in the world among the population under the age of 45 and bleeding is the dominant cause of early mortality in one third of all injured. Coagulopathy in trauma is directly related to the outcome and is considered to be the most significant preventable cause of death. Trauma-induced coagulopathy is a complex, multifactorial disorder that can be roughly divided into three phases. The entity of acute traumatic coagulopathy is characterized as an endogenous hemostatic disorder that occurs in the first few minutes of injury associated with tissue damage caused by severe trauma and hemorrhagic shock, regardless of external factors. The pathogenesis of trauma-induced coagulopathy is not fully known and is still the subject of research.

According to the latest recommendations of the European Guide for the Management of Massive Bleeding and Coagulopathy in Trauma, tranexamic acid should be used as soon as possible, and no later than three hours after the injury in a patient who is bleeding or at risk of significant bleeding. Its prehospital application should be considered.

In the light of new knowledge, the question of the justification and safety of the free use of tranexamic acid in trauma has been raised.

The use of tranexamic acid in trauma-induced coagulopathy is a simple and affordable therapeutic approach that should be used in the prehospital period in those patients who are bleeding or at risk of significant bleeding. The implementation of this therapy in our country has not yet come to life.

Keywords: trauma; trauma-induced coagulopathy; tranexamic acid; prehospital use

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Sažetak: Trauma je i danas vodeći uzrok smrti u svetu kod populacije mlađe od 45 godina, a iskrvarenje jedan od najdominantnijih uzroka rane smrtnosti kod trećine povređenih. Koagulopatija u traumi je u direktnoj vezi sa ishodom i smatra se najznačajnijim preventabilnim uzrokom smrti. Traumom indukovana koagulopatija je kompleksan, multifaktorijski poremećaj koji se grubo može podeliti na tri faze. Entitet akutne traumatske koagulopatije karakteriše se kao endogeni poremećaj hemostaze koji nastaje u prvih nekoliko minuta od povrede udruženo sa oštećenjem tkiva izazvanim teškom traumom i hemoragijskim šokom, a nezavisno od spoljašnjih faktora. Patogeneza traumom indukovane koagulopatije nije sasvim poznata i još uvek je predmet istraživanja.

Prema poslednjim preporukama Evropskog vodiča za menadžment masivnog krvarenja i koagulopatije u traumi, traneksamična kiselina treba da se primeni što je pre moguće, a najkasnije za do tri sata od povrede kod pacijenta koji krvori ili je u riziku od značajnog krvarenja. Treba razmotriti njenu prehospitalnu primenu.

U svetlu novih saznanja postavlja se pitanje opravdanosti i bezbednosti slobodne primene traneksamične kiseline u traumi.

Primena traneksamične kiseline u traumom indukovanoj koagulopatiji je jednostavan i pristupačan terapijski pristup koji bi trebalo primeniti u prehospitalnom periodu kod onih pacijenata koji krvare ili su u riziku od značajnog krvarenja. Implementacija ove terapije u našoj zemlji još nije zaživela.

Cljučne reči: trauma; traumom indukovana koagulopatija; traneksamična kiselina; prehospitalna primena

Trauma je i danas vodeći uzrok smrti u svetu kod populacije mlađe od 45 godina.¹ Uz kraniocerebralne povrede, koje su primarno odgovorne za kasniji mortalitet, nalazi se iskrvarenje kao dominantni uzrok rane smrtnosti kod trećine svih povređenih. Nekontrolisano krvarenje, kao rezultat udruženog hirurškog i koagulopatskog krvarenja, već u prehospitalnim uslovima rezultuje letalnim ishodom kod 45% traumatizovanih pacijenata.²

Koagulopatija u traumi je u direktnoj vezi sa ishodom i smatra se najznačajnijim preventabilnim uzrokom smrti.³ Već na prijemu u bolnicu 20–30% pacijenata ima znake koagulopatije.⁴ Traumom indukovana koagulopatija (TIK) je kompleksan, multifaktorijski poremećaj koji se grubo može podeliti na tri faze. Prvo, odmah po povređivanju nastaje primarna, traumom indukovana endogena faza koja odgovara akutnoj traumatskoj koagulopatiji (ATK). Druga faza podrazumeva poremećaje hemostaze nastale sekundarno, usled delovanja spoljašnjih faktora. Treća etapa nastaje po zaustavljenom krvarenju i odnosi se na posttraumatsko hiperkoagulabilno stanje sa predispozicijom nastanka tromboembolijskih komplikacija.⁵ Iako još uvek nedo-

staje jasna definicija, entitet akutne traumatske koagulopatije (ATK) karakteriše se kao endogeni poremećaj hemostaze koji nastaje u prvim nekoliko minuta od povrede udruženo sa oštećenjem tkiva izazvanim teškom traumom i hemoragijskim šokom, a nezavisno od spoljašnjih faktora. Usled masivnog oštećenja endotela i hipoperfuzije dolazi do ekscesivne aktivacije kako prokoagulantnih tako i antikoagulantnih mehanizama i hiperfibrinolize već u prehospitalnim uslovima.⁶ Na ovu komponentu koagulopatije nadovezuju se poremećaji hemostaze izazvani spoljašnjim faktorima i terapijskim delovanjem koji rezultuju hipotermijom, hipokalcijemijom, hemodilucijom i acidozom. Oni, zajedno sa ATK, sistemskim inflamatornim odgovorom na tkivno oštećenje i predisponirajućim faktorima definišu traumom indukovanu koagulopatiju (TIK).⁷ TIK je povezana sa višom incidencijom krvarenja, većim potrebama za transfuzijom, značajno višim morbiditetom (infekcija, ALI, MODS), produženjem hospitalizacije i mortalitetom od oko 50%.⁸⁻¹¹

Patofiziološki mehanizmi koagulopatije u traumi

Patogeneza traumom indukovane koagulopatije nije sasvim poznata i još uvek je predmet istraživanja ali se u poslednje vreme akcentuje neophodnost prisustva udruženih faktora, uključujući i one jatrogene, pre nego dominacija jednog puta u tom procesu. Teška trauma dovodi do ATK aktivacijom proteina C, oštećenjem glikokaliksa, disfunkcijom trombocita i deplecijom fibrinogena.¹²

Po povređivanju usled aktivacije simpatikusa, hipoperfuzije i sistemskog inflamatornog odgovora dolazi do oslobađanja kateholamina i inflamatornih medijatora u cirkulaciju koji aktiviraju endotel. Poznato je da je oštećenje endotela prvi korak za pokretanje prokoagulantnih mehanizama i nastanak trombina, međutim, njegova površina na kojoj se nalaze receptori za protein C i komponente glikokaliksa je antikoagulantna, ima ulogu u lokalizaciji i sprečavanju sistemske aktivacije koagulacije.¹³

Aktivirani protein C ima esencijalnu ulogu u nastanku ATK. Protein C se u prisustvu trombin-trombomodulin kompleksa i proteina S vezuje za svoje receptore na endotelnim ćelijama, čime postaje aktivan. Aktivacija trombomodulin-protein C sistema u teškoj traumi sa šokom rezultuje redukcijom trombina (u nekom stepenu) i inhibitora aktivatora plazminogena (PAI-1).^{14,15}

Oštećenjem glikokaliksa dolazi do oslobađanja njegovih antikoagulantnih komponenti, hondroitin-sulfata i heparan-sulfata, koji povećavaju efikasnost trombomodulina i antitrombina i dovode do „autoheparinizacije”.¹³ Uočeno je da stepen destrukcije glikokaliksa korelira sa težinom traume; pacijenti sa teškom traumom i većom destrukcijom glikokaliksa takođe imaju i veće koncentracije trombomodulina, niže vrednosti proteina C i izraženiju hiperfibrinolizu.¹⁶

Trombociti su najodgovorniji za čvrstinu formiranog ugruška u procesu hemostaze.¹⁷ Iako traumatizovani pacijenti na prijemu u bolnicu imaju uglavnom normalan

broj trombocita, pokazano je da je njihova funkcija često oštećena. Smatra se da inicijalna hiperaktivacija trombocita, kao rezultat oslobađanja ADP-a iz oštećenih ćelija, endotela, dovodi do njihovog "iscrpljivanja". U studiji koja je ispitivala broj i funkciju trombocita u prvih 30 minuta od povređivanja, ADP inhibicija trombocita dokazana je tromboelastografijom kod 86% pacijenata, a disfunkcija u odgovoru na arahidonsku kiselinu kod 45%.¹⁸ ADP inhibicija dalje uzima učešća u hiperfibrinolizi posredovanju tkivnim aktivatorom plazminogena.¹⁹

Teška trauma i hipoperfuzija, kao i prisustvo nepovoljnih spoljašnjih faktora (hipotermija i primena kristaloida) u direktnoj su vezi sa niskim koncentracijama fibrinogena na prijemu. Osim snižene produkcije, do ovog dolazi i usled povećane razgradnje u hiperfibrinolizi.¹³

Fibrinoliza je proces degradacije fibrinske mreže plazminom koji nastaje aktivacijom plazminogena tkivnim aktivatorom (t-PA), odnosno urokinaza aktivatorom plazminogena (u-PA). Paralelno sa aktivacijom proteina C, oštećenje tkiva dovodi do povećanog oslobađanja t-PA, pa će se u cirkulaciji naći visoke vrednosti t-PA i niske vrednosti PAI-1 koje vode u hiperfibrinolitičko stanje. Akutno oslobađanje t-PA rezultuje aktivacijom plazmina i posledičnom degradacijom fibrinogena i fibrina. Aktivacija koagulacije, odnosno stvoreni trombin takođe stimuliše produkciju t-PA. Aktivnost PAI-1 ostaje ista i nekoliko sati od povrede i to vreme, nazvano „antifibrinolitički proces“, verovatno značajno utiče na fibrinolitičko stanje.^{20,21}

Hiperfibrinoliza je prisutna kod oko 20% povređenih na prijemu u bolnicu.²² Njen značaj ogleda se u visokoj stopi ranog mortaliteta kod traumatizovanih pacijenata koja je potencijalno preventabilna, a ne u njenoj incidenciji. Naime, postoje tri moguća fenotipa kod teške traume prisutna na prijemu u bolnicu – pacijenti sa hiperfibrinolitičkim fenotipom, sa fiziološkom lizom i prokoagulantnim stanjem, odnosno odsustvom fibrinolize koje se u literaturi naziva *fibrinolytic shutdown*.²³ U multicentričnoj prospektivnoj opservacionoj studiji, koja je uključivala 2.450 pacijenata podeljenih u tri kategorije bazirano na stepenu lize ugruška merenog tromboelastografijom, pokazana je najveća učestalost upravo fenotipa sa odsustvom lize – kod 46% ispitanika (i mortalitetom od 22%) koju sledi fenotip sa fiziološkom lizom sa 36% (mortalitet 14%) i, naposljetku, hiperfibrinolitički fenotip sa 18% i sa najvećim mortalitetom od 34%.²⁴ Nedavno objavljeni podaci sugerišu da pacijenti sa hiperfibrinolitičkim fenotipom umiru u prva 24h od prijema ili prelaze u prokoagulantni fenotip. Nasuprot tome, 70% pacijenata sa *fibrinolytic shutdown* fenotipom perzistira sa odsustvom lize do 120 časova po prijemu. Dok hiperfibrinolitički fenotip nosi najveći mortalitet u prva 24h, *fibrinolytic shutdown*, koji perzistira 24h, povezan je sa većim kasnim mortalitetom.²⁵ Na osnovu navedenih dokaza, ako se sa jedne strane nalazi prokoagulantno stanje sa eventualnim rizikom nastanka tromboembolijskih komplikacija, a sa druge hiperfibrinoliza koja tokom vreme navodi u hiperkoagulabilnost ili smrtni ishod, postavlja se pitanje da li je uniformna hemostatska terapija adekvatna ili zahteva individualni pristup.

Traneksamična kiselina – aktuelne preporuke

Traneksamična kiselina (trans-4-aminomethyl cyclohexane-1-carboxylic acid, *Tranexamic Acid*, TXA) je sintetski analog lizina koji je kompetitivni inhibitor plazminogena i u većim dozama nekompetitivni inhibitor plazmina. Vezujući se za plazmin sprečava njegovo vezivanje za fibrin i sledstvenu fibrinolizu.²⁶ Međutim, u in vitro uslovima pokazalo se da TXA u preporučenim dozama ima različito delovanje na t-PA i u-PA aktivaciju plazminogena i da može potencirati u-PA posredovanu fibrinolizu.²⁷ Ovo bi moglo objasniti zašto primena TXA nakon tri sata od povređivanja ne daje očekivane rezultate.

U krvi brzo po i.v primeni TXA postiže maksimalne koncentracije koje potom padaju multieksponencijalno, u malom procentu vezuje se za proteine plazme (plazminogen), distribuira se u sva tkiva i telesne tečnosti, izlučuje urinarnom ekskrecijom uglavnom nepromenjena, a poluvreme eliminacije je oko 120 minuta. U antifibrinolitičkim dozama, u različitim tkivima ostaje i do 17h, dok se u serumu nalazi oko do osam sati. Neželjeni efekti kao što su hipotenzija i konvulzije mogu se izbeći sporom primenom, odnosno adekvatnim doziranjem.

Prema poslednjim preporukama Evropskog vodiča za menadžment masivnog krvarenja i koagulopatije u traumi, traneksamična kiselina treba da se primeni što je pre moguće, a najkasnije za do tri sata od povrede kod pacijenta koji krvari ili je u riziku od značajnog krvarenja. Inicijalnu dozu traneksamične kiseline od 1g (u i.v infuziji trajanja od 10 minuta) prati i.v infuzija od 1g tokom narednih osam časova. Takođe, primena TXA ne treba da čeka na rezultate visokoelastičnih testova već, naprotiv, treba razmotriti njenu prehospitálnu primenu.²⁶

Ove preporuke su dominantno bazirane na CRASH-2 studiji koja je sprovedena na više od 20.000 traumatizovanih pacijenata sa krvarenjem ili u riziku od značajnog krvarenja. Ispitujući efekte rane primene TXA, rizik od nastanka tromboembolijskih komplikacija i primenu krvi i njenih derivata, pokazala je da primena TXA smanjuje rizik od mortaliteta bilo kog uzroka tokom 28 dana od povrede ali bez značajne razlike u primenjenim transfuzijama kao i u učestalosti venskog tromboembolizma.²⁸ Detaljnija analiza podgrupe u studiji pokazala je da primena TXA u prva tri sata od povrede smanjuje rizik od smrtnog ishoda usled krvarenja i to značajno ukoliko se da u prvom satu (2.5%); odatle preporuka eksperata da se prva doza TXA da već tokom transporta do bolnice. Nasuprot tome, pokazano je da primena TXA van tročasovnog prozora povećava ovaj rizik za 1,3%.²⁹

Prateći protokol prethodne studije, CRASH-3 studija ispitivala je efekte primene TXA u prva tri sata od izolovane intracerebralne povrede (isključujući pacijente sa GCS 3 i dilatiranim zenicama). Pokazala je da je rizik od smrtnog ishoda kod blagih i srednje teških povreda značajno niži u grupi koja je primila TXA, naročito kod ranije primene, a bez značajne razlike u ishodu kod teških intracerebralnih povreda. I ovde rezultati nisu pokazali značajnu razliku u pogledu tromboembolijskih komplikacija niti konvulzija.³⁰

Oslanjajući se na rezultate CRASH studija ipak treba imati u vidu njihove razmere, odnosno različitost uslova u kojima su sprovedene (budući da se radi o velikom broju država učesnica, centara sa lokalnim protokolima za zbrinjavanje, dijagnostiku i nadoknadu kod traumatizovanih pacijenata), subjektivnost procene rizika od krvarenja, uniformnost primenjene doze i otežano izdvajanje podataka o prehospitalnoj primeni TXA. Ovakav kritički osvrt postavlja nova pitanja o primeni TXA u traumi na koja treba odgovoriti. U preporukama aktuelnog Evropskog vodiča za menadžment masivnog krvarenja i koagulopatije u traumi, baziranog na podacima CRASH studija, kliničaru je ostavljena procena „masivnog krvarenja i rizika od značajnog krvarenja”, što indikaciono područje ostavlja širokim i nejasno definisanim, a to dalje postavlja pitanje bezbednosti primene.

Indikacija za primenu TXA

Pitanje od najvećeg značaja jeste kome zapravo treba TXA ili kako pretpostaviti hiperfibrinolizu još u prehospitalnim uslovima. Kako je najveći procenat smrtnosti u traumi vezan upravo za *fibrinolytic shutdown* fenotip, prirodno se javila bojazan da slobodna primena TXA nije uvek primerena. Primećeno je da postoji rizik od nastanka mikrotromboza kod pacijenata sa fiziološkom lizom ili njenim odsustvom.³¹ Takođe, prema nadavno objavljenoj studiji, primena TXA u traumi u vezi je sa nastankom multiple organske disfunkcije (*Multiple Organ Failure*, MOF) kod hiperfibrinolitičkog i "fibrinolytic shutdown" fenotipa.³² Iako još uvek nema većih studija koje bi potvrdile ove podatke postavljeno je pitanje opravdanosti primene TXA bez prethodno učinjenih viskoelastičnih testova. Sa druge strane posmatrano, ATK je brz, dinamičan proces koji ne može da čeka na rezultate testova. Plazmin-tromboelastografija (TEG) je nedavno predstavljen kao novi test tromboelastografije koji za vreme od pet minuta može stratifikovati pacijente sa rizikom od hiperfibrinolize.³³ U budućnosti bi ovako brzi testovi mogli rešiti problem prave indikacije za TXA.

Efekti rane primene TXA

Na osnovu dosad poznatih patofizioloških mehanizama, ATK je proces koji započinje gotovo odmah po povređivanju i hiperfibrinoličko stanje bi trebalo prevenirati ranom primenom TXA. Iako je smrtnost usled krvarenja u traumi najveća u prehospitalnim uslovima, preporuke evropskog vodiča o jednostavnoj primeni TXA u prvom „zlatnom satu” nisu zaživele u celosti.

Nedavna multicentrična randomizovana studija ROC-TXA pratila je efekte rane primene TXA kod izolovane umereno teške i teške intrakranijalne povrede na mortalitet nakon 28 dana i neurološki ishod nakon perioda od šest meseci.³⁴ Iako rezultati nisu pokazali značajnu razliku između primene TXA i placeba, ova studija je prvo

veliko prehospitalno istraživanje od značaja. Uključila je 1.063 pacijenta kojima je ordinirana TXA na osnovu GCS, a pre učinjene dijagnostike pokazala je da nije jednostavno dizajnirati odgovarajuće istraživanje o prehospitalnoj primeni jer je na taj način uključila ne samo izrazito teške povrede u kojima malo verovatno TXA može imati efekta, već i kome drugih uzroka.

Za ovom studijom usledila je nova multicentrična randomizovana studija u SAD koja je ispitivala bezbednost i efekte primene TXA u dozi od 1g u okviru prva dva sata od povrede, odnosno tokom transporta do prvog trauma centra kod pacijenata u riziku od krvarenja. Uključeni su pacijenti sa hipotenzijom i tahikardijom. Rezultati nisu pokazali uticaj na tridesetodnevni mortalitet osim kod posebne kategorije pacijenata. Kod onih kod kojih je hemoragijski šok bio ozbiljniji (sistolni krvni pritisak ≤ 70 mmHg), kao i kod primene u okviru prvog sata, mortalitet je bio značajno niži.³⁵ Subjektivnost procene rizika od krvarenja zamerena CRASH studijama ovakvim dizajnom je donekle prenebregnuta i ova, kao i studije koje su u toku, mogle bi dopuniti postojeće preporuke.

Istovremena primena TXA i drugih faktora koagulacije u TIK-u

Kako je fibrinogen najosetljiviji na spoljašnje faktore, najbrže mu opada koncentracija u TIK-u. Odatle ne čude dokazi da rana nadoknada fibrinogena dovodi do redukcije krvarenja, potreba za transfuzijom i mortaliteta.³⁶ Velika multicentrična retrospektivna studija MATTERS sprovedena u vojnim uslovima pokazala je benefit od jedne doze TXA na preživljavanje ali još veći benefit ukoliko se primeni sa krioprecipitatom.³⁷ Ovo je probudilo interesovanje za primenu drugih faktora sa TXA u prehospitalnim uslovima. Trenutno je u fokusu primena koncentrata fibrinogena koji bi bio vrlo jednostavno primenljiv u prehospitalnim uslovima u odnosu na krioprecipitat. Rezultati studija koje su u toku i ispituju njihovu primenu (FEISTY, ProoF-iTH i CRYOSTAT-2 studija) se očekuju.

Primena sveže smrznute plazme u terapiji TIK-a u vojnim uslovima u PAMPer studiji pokazala je značajno niži mortalitet u grupi pacijenata koji su u riziku od hemoragijskog šoka, a transportuju se do trauma-centra duže od 20 minuta.³⁸ Kako u civilnim uslovima ovo nije praktično izvodljiva terapijska mera, postavlja se pitanje da li bi primena protrombinskog kompleksa, uprkos velikom trombogenom potencijalu, mogla naći mesta u terapiji TIK-a.

Bezbednost primene TXA

Rizik od razvoja tromboembolijskih komplikacija vezanih za primenu TXA u CRASH studiji nije bio povišen u odnosu na placebo.²⁹ Za razliku od toga, rezultati

MATTERS studije pokazali su značajno veću učestalost tromboze dubokih vena nogu i plućne tromboembolije.³⁹ Ovakva razlika u rezultatima se delimično može objasniti većim stepenom povrede i opsežnijom prehospitalnom nadoknadom u vojnim u odnosu na civilne uslove povređivanja. Takođe, pitanje vremena u kojem se primenjuje TXA može biti od važnosti jer je kod teških trauma najčešći *fibrinolytic shutdown* fenotip. U svakom slučaju, teoretski rizik od tromboembolijskih komplikacija ne bi trebalo da prevagne u odnosu na jasnu dobrobit od rane primene TXA u traumatskoj koagulopatiji ali ne treba biti zanemaren naročito uz primenu drugih protrombogenih faktora.⁴⁰

U kardiohirurgiji gde se primenjuju visoke doze TXA (80-100mg/kg) konvulzije su poznat, dozno-zavisan, neželjeni efekat. Smatra se da je mehanizam nastanka inhibicija centralnih glicinskih i GABA A receptora i da efekat može biti ublažen lekovima koji modulišu njihovu aktivnost, a potenciran renalnom insuficijencijom ili oštećenjem hematoencefalne barijere.⁴¹ Preporuka za primenu bolusne doze od 1g praćene osmočasovnom infuzijom još 1g TXA dolazi iz *Cochrane*-ove baze podataka iz 2007. godine o primeni antifibrinolitike terapije u hirurgiji bez posebnog osvrta na traumatu.⁴² U ROC-TXA studiji, međutim, primećeno je da je učestalost konvulzija bila značajno veća u grupi pacijenata kojima je ordiniran bolus od 2g TXA u odnosu na grupe koje su primile dozu od 1g, odnosno placebo.³⁴ Iako je preporučena doza bezbedna, ispod praga za pojavu konvulzija, još uvek nedostaju podaci o tome da li bi individualno doziranje bilo efikasnije od empirijske primene leka.

Zaključak

Primena TXA kiseline u traumom indukovanoj koagulopatiji je jednostavan i pristupačan terapijski pristup koji bi trebalo primeniti u prehospitalnom periodu kod onih pacijenata koji krvare ili su u riziku od značajnog krvarenja. Implementacija ove terapije u našoj zemlji još nije zaživela.

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TRANEXAMIC ACID IN TRAUMA-INDUCED COAGULOPATHY

Summary: Trauma is still the leading cause of death in the world among the population under the age of 45 and bleeding is the dominant cause of early mortality in one third of all injured. Coagulopathy in trauma is directly related to the outcome and is considered to be the most significant preventable cause of death. Trauma-induced coagulopathy is a complex, multifactorial disorder that can be roughly divided into three phases. The entity of acute traumatic coagulopathy is characterized as an endogenous hemostatic disorder that occurs in the first few minutes of injury associated with tissue damage caused by severe trauma and hemorrhagic shock, regardless of external factors. The pathogenesis of trauma-induced coagulopathy is not fully known and is still the subject of research.

According to the latest recommendations of the European Guide for the Management of Massive Bleeding and Coagulopathy in Trauma, tranexamic acid should be used as soon as possible, and no later than three hours after the injury in a patient who is bleeding or at risk of significant bleeding. Its prehospital application should be considered.

In the light of new knowledge, the question of the justification and safety of the free use of tranexamic acid in trauma has been raised.

The use of tranexamic acid in trauma-induced coagulopathy is a simple and affordable therapeutic approach that should be used in the prehospital period in those patients who are bleeding or at risk of significant bleeding. The implementation of this therapy in our country has not yet come to life.

Keywords: trauma; trauma-induced coagulopathy; tranexamic acid; prehospital use

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Sažetak: Trauma je i danas vodeći uzrok smrti u svetu kod populacije mlađe od 45 godina, a iskrvarenje jedan od najdominantnijih uzroka rane smrtnosti kod trećine povređenih. Koagulopatija u traumi je u direktnoj vezi sa ishodom i smatra se najznačajnijim preventabilnim uzrokom smrti. Traumom indukovana koagulopatija je kompleksan, multifaktorijski poremećaj koji se grubo može podeliti na tri faze. Entitet akutne traumatske koagulopatije karakteriše se kao endogeni poremećaj hemostaze koji nastaje u prvih nekoliko minuta od povrede udruženo sa oštećenjem tkiva izazvanim teškom traumom i hemoragijskim šokom, a nezavisno od spoljašnjih faktora. Patogeneza traumom indukovane koagulopatije nije sasvim poznata i još uvek je predmet istraživanja.

Prema poslednjim preporukama Evropskog vodiča za menadžment masivnog krvarenja i koagulopatije u traumi traneksamična kiselina treba da se primeni što je pre moguće, a najkasnije za do tri sata od povrede kod pacijenta koji krvar ili je u riziku od značajnog krvarenja. Treba razmotriti njenu prehospitalnu primenu.

U svetlu novih saznanja postavlja se pitanje opravdanosti i bezbednosti slobodne primene traneksamične kiseline u traumi.

Primena traneksamične kiseline u traumom indukovanoj koagulopatiji je jednostavan i pristupačan terapijski pristup koji bi trebalo primeniti u prehospitalnom periodu kod onih pacijenata koji krvare ili su u riziku od značajnog krvarenja. Implementacija ove terapije u našoj zemlji još nije zaživela.

Ključne reči: trauma; traumom indukovana koagulopatija; traneksamična kiselina; prehospitalna primena

Trauma is still the leading cause of death in the world among the population under the age of 45.¹ In addition to traumatic brain injuries (TBI), which are primarily responsible for later mortality, bleeding is the dominant cause of early mortality in one third of all injured. Uncontrolled bleeding, as a result of combined surgical and coagulopathic bleeding, already in prehospital conditions results in a lethal outcome in 45% of traumatized patients.²

Coagulopathy in trauma is directly related to the outcome and is considered to be the most significant preventable cause of death.³ Already on admission to the hospital, 20-30% of patients have signs of coagulopathy.⁴ Trauma-induced coagulopathy (TIC) is a complex, multifactorial disorder that can be roughly divided into three phases. First, the primary, trauma-induced endogenous phase corresponding to acute traumatic coagulopathy (ATC), occurs immediately after injury. The second phase involves disorders of hemostasis that occur secondarily, due to the action of external factors. The third stage occurs after the bleeding has stopped and refers to the post-traumatic

hypercoagulable condition with a predisposition to thromboembolic complications.⁵ Although a clear definition is still lacking, the entity of acute traumatic coagulopathy (ATC) is characterized as an endogenous hemostatic disorder that occurs in the first few minutes of injury associated with tissue damage caused by severe trauma and hemorrhagic shock, regardless of external factors. Due to massive endothelial damage and hypoperfusion, there is excessive activation of both procoagulant and anticoagulant mechanisms and hyperfibrinolysis even in prehospital conditions.⁶ This component of coagulopathy is followed by hemostatic disorders caused by external factors and therapeutic effects that result in hypothermia, hypocalcemia, hemodilution and acidosis. They, together with ATC, systemic inflammatory response to tissue damage and predisposing factors, define trauma-induced coagulopathy (TIC).⁷ TIC is associated with a higher incidence of bleeding, transfusion requirements, significantly higher morbidity (infection, ALI, MODS), length of hospital stay, and mortality of about 50%.⁸⁻¹¹

Pathophysiological mechanisms of coagulopathy in trauma

The pathogenesis of trauma-induced coagulopathy is not fully known and is still the subject of research, but recently the necessity of the presence of associated factors, including iatrogenic ones, has been emphasized, rather than the domination of one path in the process. Severe trauma leads to ATK by protein C activation, glycocalyx damage, platelet dysfunction, and fibrinogen depletion.¹²

Upon injury due to sympathetic activation, hypoperfusion, and systemic inflammatory response, catecholamines and inflammatory mediators are released into the circulation that activate the endothelium. Endothelial damage is known to be the first step in initiating procoagulant mechanisms and thrombin formation, however, its surface on which protein C receptors and glycocalyx components are located is anticoagulant, and has a role in localizing and preventing systemic activation of coagulation.¹³

Activated protein C plays an essential role in the formation of ATK. Protein C binds to its receptors on endothelial cells in the presence of thrombin-thrombomodulin complex and protein C, thus becoming active. Activation of the thrombomodulin-protein C system in severe shock trauma results in a reduction in thrombin (to some extent) and plasminogen activator inhibitor-1 (PAI-1).^{14,15}

Damage to the glycocalyx leads to the release of its anticoagulant components, chondroitin sulfate and heparan sulfate, which increase the efficiency of thrombomodulin and antithrombin and lead to "autoheparinization".¹³ It has been observed that the degree of glycocalyx destruction correlates with the severity of the trauma; patients with severe trauma and greater glycocalyx destruction also have higher thrombomodulin concentrations, lower protein C values, and more pronounced hyperfibrinolysis.¹⁶

Platelets are most responsible for the firmness of the formed clot in the process of hemostasis.¹⁷ Although traumatized patients on admission to the hospital generally have a normal platelet count, it has been shown that their function is often impaired. It is believed that the initial hyperactivation of platelets as a result of the release of ADP from damaged endothelial cells leads to their "exhaustion". In a study that examined platelet count and function in the first 30 minutes of injury, platelet ADP inhibition was demonstrated by thromboelastography in 86% of patients and arachidonic acid response dysfunction in 45%.¹⁸ ADP inhibition further participates in tissue plasminogen activator-mediated hyperfibrinolysis.¹⁹

Severe trauma and hypoperfusion, as well as the presence of adverse external factors (hypothermia and crystalloid application) are directly related to low concentrations of fibrinogen at admission. In addition to reduced production, this also occurs due to increased degradation in hyperfibrinolysis.¹³

Fibrinolysis is the process of degradation of the fibrin mesh by plasmin, generated by activation of plasminogen tissue activator (t-PA) or urokinase plasminogen activator (u-PA). In parallel with the activation of protein C, tissue damage leads to increased release of t-PA, so high values of t-PA and low values of PAI-1 will be found in the circulation, leading to a hyperfibrinolytic state. Acute release of t-PA results in plasmin activation and consequent degradation of fibrinogen and fibrin. Activation of the coagulation or thrombin generated also stimulates the production of t-PA. The activity of PAI-1 remains the same for several hours after the injury and that time, called the "antifibrinolytic gap", probably significantly affects the fibrinolytic state.^{20,21}

Hyperfibrinolysis is present in about 20% of injured on admission to the hospital.²² Its significance is reflected in the high rate of early mortality in traumatized patients, which is potentially preventable, and not in its incidence. Namely, there are three possible phenotypes in severe trauma present at hospital admission - patients with hyperfibrinolytic phenotype, with physiological lysis and procoagulant condition or absence of fibrinolysis, which in the literature is called "fibrinolytic shutdown".²³ A multicenter prospective observational study involving 2,450 patients divided into three categories based on the degree of lysis of the clot measured by thromboelastography showed the highest incidence of the phenotype with no lysis - in 46% of subjects (and mortality of 22%) followed by phenotype with physiological lysis, in 36% (mortality 14%) and finally, the hyperfibrinolytic phenotype with 18% and with the highest mortality of 34%.²⁴ Recently published data suggest that patients with the hyperfibrinolytic phenotype die within the first 24 h of admission or switch to the procoagulant phenotype. In contrast, 70% of patients with the "fibrinolytic shutdown" phenotype persist with the absence of lysis for up to 120 hours after admission. While the hyperfibrinolytic phenotype carries the highest mortality in the first 24 h, "fibrinolytic shutdown" that persists for 24 h is associated with higher late mortality.²⁵ Based on the above evidence, if on the one hand there is a procoagulant condition with a

possible risk of thromboembolic complications, and on the other hyperfibrinolysis which over time leads to hypercoagulability or death, the question arises whether uniform hemostatic therapy is adequate or requires an individual approach.

Tranexamic acid – current recommendations

Tranexamic acid (trans-4-aminomethyl cyclohexane-1-carboxylic acid, Tranexamic Acid, TXA) is a synthetic lysine analogue that is a competitive plasminogen inhibitor and in higher doses a non-competitive plasmin inhibitor. By binding to plasmin, it prevents its binding to fibrin and consequent fibrinolysis.²⁶ However, in in-vitro conditions, TXA at the recommended doses has been shown to have different effects on t-PA and u-PA activation of plasminogen and may potentiate u-PA-mediated fibrinolysis.²⁷ This could explain why applying TXA three hours after injury does not give the expected results.

In the blood, after TXA administration, it reaches maximum concentrations which then fall multiexponentially, it binds to a small percentage of plasma proteins (plasminogen), is distributed to all tissues and body fluids, excreted by urinary excretion mostly unchanged, and the elimination half-life is about 120 minutes. In antifibrinolytic doses, it remains in various tissues for up to 17 hours, while it remains in the serum for up to eight hours. Side effects such as hypotension and convulsions can be avoided by slow administration or adequate dosing.

According to the latest recommendations of the European Guide for the Management of Massive Bleeding and Coagulopathy in Trauma, tranexamic acid should be used as soon as possible, and no later than three hours after the injury in a patient who is bleeding or at risk of significant bleeding. The initial dose of tranexamic acid of 1 g (in i.v infusion lasting 10 minutes) is followed by i.v infusion of 1g in the next eight hours. Also, the application of TXA should not wait for the results of viscoelastic tests, but on the contrary, its prehospital application should be considered.²⁶

These recommendations are predominantly based on a CRASH-2 study conducted on more than 20,000 traumatized patients with bleeding or at risk of significant bleeding. Examining the effects of early TXA administration, the risk of thromboembolic complications and the use of blood and its derivatives, showed that TXA administration reduced the risk of mortality of any cause within 28 days of injury but without significant difference in transfusions and venous thromboembolism.²⁸ A more detailed analysis of the subgroup in the study showed that the application of TXA in the first three hours after injury reduces the risk of death due to bleeding, and this is significant if given in the first hour (2.5%); hence the expert's recommendation that the first dose of TXA be given during transport to the hospital. In contrast, application of TXA outside the three-hour window has been shown to increase this risk by 1.3%.²⁹

Following the protocol of the previous study, the CRASH-3 study examined the effects of TXA administration in the first three hours of isolated TBI (excluding patients with GCS 3 and dilated pupils). It showed that the risk of death in mild and moderate injuries was significantly lower in the group receiving TXA, especially in earlier administration, and without a significant difference in outcome in severe intracerebral injuries. Here, too, the results showed no significant difference in terms of thromboembolic complications or convulsions.³⁰

Relying on the results of CRASH studies, however, one should keep in mind their scale or the diversity of conditions in which they were conducted (given the large number of participating countries, centers with local protocols for care, diagnosis and volume replacement therapy of traumatized patients), the subjectivity of bleeding risk assessment, uniformity of the administered dose and difficult extraction of data on prehospital administration of TXA. This critical review raises new questions about the application of TXA in trauma that need to be answered. The recommendations of the current European guide for the management of massive bleeding and coagulopathy in trauma based on CRASH study data left the clinician with an assessment of "massive bleeding and risk of significant bleeding", which leaves the indication area wide and unclear, which further raises the question of safety.

Indications for the use of TXA

The most important question is who actually needs TXA or how to assume hyperfibrinolysis even in prehospital conditions. As the highest mortality rate in trauma is related to the "fibrinolytic shutdown" phenotype, there is a natural fear that the free use of TXA is not always appropriate. It has been observed that there is a risk of developing microthrombosis in patients with physiological lysis or its absence.³¹ Also, according to recently published study, administration of TXA following traumatic injury was associated with multiple organ failure (MOF) in the fibrinolysis shutdown and hyperfibrinolysis phenotypes.³² Although there are still no major studies to confirm these data, the question of the justification of the use of TXA without previously performed viscoelastic tests has been raised. On the other hand, ATC is a fast, dynamic process that cannot wait for test results. Plasmin thromboelastography (TEG) was recently introduced as a new thromboelastography test that can stratify patients at risk of hyperfibrinolysis over a period of five minutes.³³ In the future, such rapid tests could solve the problem of the right indication for TXA.

Effects of early TXA administration

Based on the pathophysiological mechanisms known so far, ATC is a process that begins almost immediately after injury and the hyperfibrinolytic condition should be

prevented by early administration of TXA. Although the mortality due to bleeding in trauma is highest in prehospital conditions, the recommendations of the European guide on the simple application of TXA in the first "golden hour" did not come to life in full.

A recent multicenter randomized study of ROC-TXA followed the effects of early TXA administration in isolated moderate to severe TBI on 28-day mortality and six-month functional neurological outcome.³⁴ Although the results did not show a significant difference between the use of TXA and placebo, this study is the first major prehospital study of significance. It included 1063 patients who were prescribed TXA based on GCS, and before the diagnosis was made, it was not easy to design an appropriate study of prehospital use because it included not only extremely severe injuries in which TXA is unlikely to have an effect, but also other causes of comas.

This study was followed by a new multicenter randomized study in the United States that examined the safety and effects of 1g TXA within the first two hours of injury or during transport to the first trauma center in patients at risk of bleeding. Included were patients with hypotension and tachycardia. The results showed no effect on thirty-day mortality except in a special category of patients. In those in whom the hemorrhagic shock was more severe (systolic blood pressure ≤ 70 mmHg) as well as in the application within the first hour, mortality was significantly lower.³⁵ The subjectivity of bleeding risk assessment as opposed to CRASH studies with this design has been somewhat neglected and this, as well as ongoing studies, could complement existing recommendations.

Simultaneous application of TXA and other coagulation factors in TIC

As fibrinogen is most sensitive to external factors, its concentration in TIC decreases the fastest. Hence, it is not surprising that early fibrinogen replacement leads to reduced bleeding, transfusion needs, and mortality.³⁶ A large multicenter retrospective study of MATTERS conducted in military conditions showed the benefit of a single dose of TXA on survival but an even greater benefit if applied with a cryoprecipitate.³⁷ This aroused interest in the application of other factors with TXA in prehospital settings. Currently, the focus is on the use of fibrinogen concentrate, which would be very easily applicable in prehospital conditions in relation to cryoprecipitate. The results of ongoing studies examining their application (FEISTY, ProoF-iTH and CRYOSTAT-2 studies) are expected.

The use of fresh frozen plasma in TIC therapy in military conditions in the PAMPer study showed significantly lower mortality in the group of patients at risk of hemorrhagic shock, who are transported to the trauma center longer than 20 minutes.³⁸ As this is not a practically feasible therapeutic measure in civilian conditions, the question arises whether the use of the prothrombin complex, despite its great thrombogenic potential, could find a place in the therapy of TIC.

TXA application safety

The risk of developing thromboembolic complications associated with the use of TXA in the CRASH study was not increased compared to placebo.²⁹ In contrast, the results of the MATTERS study showed a significantly higher incidence of deep vein thrombosis and pulmonary thromboembolism.³⁹ This difference in results can be partly explained by the higher degree of injury and more extensive pre-hospital replacement therapy in the military in relation to civilian injury conditions. Also, the question of the time at which TXA is administered may be important because in severe trauma the most common phenotype is the "fibrinolytic shutdown" phenotype. In any case, the theoretical risk of thromboembolic complications should not outweigh the clear benefit from early administration of TXA in traumatic coagulopathy but should not be neglected especially with the use of other prothrombogenic factors.⁴⁰

In cardiac surgery where high doses of TXA (80-100mg / kg) are used, convulsions are a known, dose-dependent, side effect. It is believed that the mechanism of occurrence is inhibition of central glycine and GABA A receptors and that the effect can be mitigated by drugs that modulate their activity, and potentiated by renal insufficiency or damage to the blood-brain barrier.⁴¹ The recommendation to administer a bolus dose of 1g followed by an eight-hour infusion of another 1g of TXA comes from Cochrane's 2007 database on the use of antifibrinolytic therapy in surgery without special reference to trauma. In the ROC-TXA study, however, it was observed that the incidence of convulsions was significantly higher in the group of patients administered a 2g TXA bolus compared to the groups receiving a 1g or placebo dose.³⁴ Although the recommended dose is safe, below the threshold for convulsions, there is still no data on whether individual dosing would be more effective than empirical drug administration.

Conclusion

The use of TXA acid in trauma-induced coagulopathy is a simple and affordable therapeutic approach that should be used in the prehospital period in those patients who are bleeding or at risk of significant bleeding. The implementation of this therapy in our country has not yet come to life.

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