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UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
FACULDADE DE MEDICINA

Welder Zamoner

Comparação quanto à eficácia e segurança de diferentes esquemas de administração de vancomicina em pacientes com injúria renal aguda em hemodiálise: um ensaio clínico randomizado

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obtenção do título de Doutor em Fisiopatologia em Clínica Médica

Orientadora: Profa. Dra. Daniela Ponce
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FICHA CATALOGRÁFICA ELABORADA PELA SEÇÃO TÉC. AQUIS. TRATAMENTO DA INFORM.
DIVISÃO TÉCNICA DE BIBLIOTECA E DOCUMENTAÇÃO - CÂMPUS DE BOTUCATU - UNESP
BIBLIOTECÁRIA RESPONSÁVEL: ROSEMEIRE APARECIDA VICENTE-CRB 8/5651

Zamoner, Welder.
Comparação quanto à eficácia e segurança de diferentes esquemas de administração de vancomicina em pacientes com injúria renal aguda em hemodiálise : um ensaio clínico randomizado / Welder Zamoner. - Botucatu, 2023

Tese (doutorado) - Universidade Estadual Paulista "Júlio de Mesquita Filho", Faculdade de Medicina de Botucatu
Orientador: Daniela Ponce
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Capes: 40101134

1. Vancomicina. 2. Injúria renal aguda. 3. Septicemia. 4. Diálise. 5. Hemodiálise.

Palavras-chave: Diálise; IRA; Injúria renal aguda; Sepse; Vancomicina.

"A tarefa não é tanto ver aquilo que ninguém viu, mas pensar o que ninguém ainda pensou sobre aquilo que todo mundo vê."

Arthur Schopenhauer

Dedicatória

À mulher da minha vida, Soraya

Minha esposa, companheira e amiga, pelo apoio incondicional e sonhos compartilhados. Por ser minha parceira e confidente, pela compreensão e estímulo em todas as escolhas e decisões. Sem a qual nenhuma conquista valeria a pena.

Aos meus pais, Valdir e Ermelinda, e ao meu irmão, Wendell

Incentivadores constantes e responsáveis por quem sou. Que dignamente apresentaram-me ao caminho da honestidade, persistência, amor e união, ensinaram-me a buscar forças, a superar obstáculos, e a doar sempre o meu melhor.

Agradecimentos especiais

À **Deus**, primeiramente, por ser autor do meu destino e meu guia, abençoando-me sempre. Por tudo que me proporcionou, pelas pessoas maravilhosas e grandes oportunidades que colocou em meu caminho, e por me dar forças para seguir sempre adiante, superando qualquer obstáculo.

À minha orientadora, **Profa. Dra. Daniela Ponce**, o meu agradecimento pelo exemplo profissional e parceria. Pela oportunidade de realizar este e tantos outros projetos ao seu lado. Alguém que inspira sabedoria, que motiva, que questiona, que estimula, sempre disposta a ouvir dúvidas e problemas, com muita paciência e constante incentivo científico, mostrando o melhor caminho a ser seguido e fornecendo todas as ferramentas para trilhá-lo. Alguém de quem muito me orgulho, por sua trajetória, conquistas e dedicação em tudo que realiza. Meu respeito, gratidão e eterna admiração. E que eu possa sempre contar com o privilégio de sua amizade.

Ao meu coorientador, **Prof. Dr. Ricardo de Souza Cavalcante**, por sua parceria e suas contribuições na construção deste projeto de pesquisa. Aos membros da banca do Exame Geral de Qualificação, **Prof. Dr. Carlos Magno C. B. Fortaleza** e **Prof. Dr. Pasqual Barretti**, que dedicaram seu tempo e conhecimento para enriquecer este trabalho.

Aos **meus queridos familiares** e **amigos**, por todo apoio, torcida, confiança e compreensão pelos momentos de ausência. Aos meus avós e tios que cumpriram sua missão cedo demais e com certeza torcem por mim e me protegem de outro plano.

Aos grandes **professores e médicos contratados da Nefrologia** que me ensinaram e ensinam Nefrologia diariamente e sempre estimularam o saber científico de maneira agradável e acolhedora.

A todos os **membros da equipe multiprofissional (família Nefro)**: médicos residentes, secretários, nutricionistas, enfermeiros, técnicos em Enfermagem, psicólogos, assistentes sociais, e aprimorandos, pelo profissionalismo e carinho com que desempenham suas funções diariamente, sempre visando manter a qualidade de atendimento e o respeito aos pacientes, o que torna esse time forte e especial. À **equipe IRA**, em especial, pela parceria, trabalho e carinho.

Ao **Hospital das Clínicas de Botucatu**, por fornecer atendimento digno e humano a quem precisa, e que, a despeito das dificuldades que enfrenta, sempre trabalha em prol dos seus pacientes.

Aos **pacientes**, principais motivadores da busca por novos saberes e razão de toda a dedicação deste trabalho.

Sumário

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Comparação quanto à eficácia e segurança de diferentes esquemas de administração de vancomicina em pacientes com injúria renal aguda em hemodiálise: um ensaio clínico randomizado

RESUMO

Introdução: Sepse é a principal causa de Injúria Renal Aguda (IRA) com necessidade dialítica em pacientes críticos, sendo a vancomicina amplamente utilizada. Sua farmacocinética e farmacodinâmica (PK/PD) sofrem alterações durante a hemodiálise (HD), aumentando o risco de concentrações subterapêuticas. **Objetivo:** Comparar diferentes protocolos de administração de vancomicina a fim de avaliar as concentrações séricas e razão área sob a curva/concentração inibitória mínima (ASC/CIM) a partir da PK/PD. **Metodologia**: Ensaio clínico randomizado, não-cego, incluindo pacientes críticos adultos, com diagnóstico de IRA séptica em HD convencional (4 horas) e prolongada (6 e 10 horas) e em uso de vancomicina há pelo menos 72horas de maio/2019 a maio/2021. Foram analisadas sessões de pacientes randomizados em 3 grupos (G): G controle (C, dose de 15mg/kg após a sessão de HD), G intervenção (I) 2 horas (dose de 7,5mg/kg na segunda hora da HD e 7,5mg/kg após a sessão) e GI infusão contínua (dose de 30mg/kg em bomba de infusão contínua, em 24 horas). Foram excluídos pacientes em diálise crônica, gestantes e com sessão interrompida por razões clínicas ou técnicas. **Resultados**: Dos 316 pacientes recrutados, 87 foram randomizados e 174 sessões de HD monitorizadas. Houve predomínio do sexo masculino (69,5%), idade 61±11anos, APACHE II 31±6, ATN-ISS 0,79±0,14. Para a análise, 28 sessões pertenciam ao GC, 47 sessões ao GI 2 horas e 31 sessões ao GI infusão contínua. Os grupos foram semelhantes quanto à idade, peso, comorbidades, escores de gravidade, uso de diurético e drogas nefrotóxicas, diurese, albumina, PCR, hematócrito, modalidade de HD, recuperação de função renal e óbito. Ao serem analisadas as sessões de HD, não houve diferença entre os grupos quanto a Kt/V, ultrafiltração, coagulação de sistema ou hipotensão. O GC apresentou maior frequência de concentração sérica subterapêutica ao término da HD em comparação com o GI 2 horas e infusão contínua (86,7% vs. 42,2% vs. 3,2%, p<0,0001), maior *clearance* dialítico (p=0,04) e menor ASC/CIM (p<0,0001). O GI infusão contínua apresentou maior frequência de concentrações supraterapêuticas (71%). Regressão logística identificou a variável concentração inicial (OR 1,16, p=0,001) como fator de risco para uma concentração não terapêutica (ASC/CIM menor que 400 mg·h/L ou maior que 600 mg·h/L) de vancomicina, enquanto que o grupo intervenção 2 horas foi identificado como fator de proteção (OR 0,24, p=0,04). **Conclusão**: Nossos resultados sugerem que administrar vancomicina durante a diálise resultou em menor proporção de concentrações supraterapêuticas ou subterapêuticas quando comparada à administração em infusão contínua ou após o término da sessão, respectivamente. Novos estudos são necessários para sugerir doses mais adequadas e avaliar o impacto desses achados nos desfechos clínicos.

Palavras-chave: sepse, injúria renal aguda, IRA, diálise, vancomicina, farmacocinética, farmacodinâmica.

ABSTRACT

Introduction: Sepsis is the main cause of Acute Kidney Injury (AKI), requiring dialysis in critically ill patients, with vancomycin being widely used. Its pharmacokinetics and pharmacodynamics (PK/PD) change during hemodialysis (HD), increasing the risk of subtherapeutic concentrations. **Objective:** To compare different vancomycin administration protocols to assess serum concentrations and area under the curve/minimum inhibitory concentration (AUC/MIC) ratio from PK/PD. **Methodology:** Randomized, non-blind clinical trial, including critically ill adults diagnosed with septic AKI on conventional (4 hours) and prolonged HD (6 and 10 hours) and using vancomycin for at least 72 hours from May/2019 to May /2021. Sessions of patients were analyzed and randomized into three groups (G): G control (C, dose of 15mg/kg after HD session), G intervention (I) 2 hours (dose of 7.5mg/kg in the second hour of HD and 7.5mg/kg after the session) and IG continuous infusion (dose of 30mg/kg in continuous infusion pump, in 24 hours). Patients on chronic dialysis, pregnant women, and those whose session was interrupted for clinical or technical reasons were excluded. **Results:** Of the 316 patients recruited, 87 were randomized, and 174 HD sessions were monitored. There was a predominance of males (69.5%), age 61±11 years, APACHE II 31±6, ATN-ISS 0.79±0.14. For the analysis, 28 sessions belonged to the CG, 47 sessions to the 2-hour IG, and 31 to the continuous infusion IG. The groups were similar in age, weight, comorbidities, severity scores, use of diuretics and nephrotoxic drugs, urine output, albumin, CRP, hematocrit, HD modality, recovery of renal function, and death. When HD sessions were analyzed, there was no difference between the groups regarding Kt/V, ultrafiltration, system coagulation, or hypotension. The CG had a higher frequency of subtherapeutic serum levels at the end of HD compared to the 2-hour IG and continuous infusion (86.7% vs. 42.2% vs. 3.2%, $p<0.0001$), higher clearance dialysis ($p=0.04$) and lower AUC/MIC ($p<0.0001$). The IG continuous infusion had a higher frequency of supratherapeutic concentrations (71%). Logistic regression identified the initial concentration variable as a risk factor (OR 1.16, $p=0.001$) for a non-therapeutic concentration (AUC/MIC less than 400 mg·h/L or greater than 600 mg·h/L) of vancomycin. In contrast, the 2-hour intervention group was identified as a protective factor (OR 0.24, $p=0.04$). **Conclusion:** Our results suggest that administering vancomycin during dialysis resulted in a lower proportion of supratherapeutic or subtherapeutic concentrations compared to administration in continuous infusion or after the end of the session, respectively. New studies are needed to suggest more appropriate doses and assess these findings' impact on clinical outcomes.

Keywords: sepsis, acute kidney injury, AKI, dialysis, vancomycin, pharmacokinetics, pharmacodynamics.

equipe de Enfermagem e pacientes e/ou familiares estavam cientes de qual esquema de administração da vancomicina havia sido randomizado, impossibilitando o cegamento. Os desfechos clínicos recuperação de função renal e mortalidade de todas as causas não foram diferentes entre os grupos controle e intervenções, porém o tamanho amostral foi insuficiente para essa conclusão. A bactéria predominante foi *Sthaphylococcus* coagulase negativo, o que também pode ter influenciado nos desfechos.

Entretanto, este foi o primeiro estudo clínico com desenho randomizado que avaliou a razão ASC/CIM durante sessões de hemodiálise tanto convencional como prolongada em pacientes sépticos com IRA sob diferentes esquemas de administração da vancomicina.

6. CONCLUSÃO

Nossos resultados sugerem que administrar vancomicina durante a diálise resultou em menor proporção de concentrações supraterapêuticas ou subterapêuticas quando comparada à administração em infusão contínua ou após o término da sessão, respectivamente. Novos estudos são necessários para sugerir doses mais adequadas e avaliar o impacto desses achados nos desfechos clínicos.

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guaranteeing therapeutic concentrations. These will be of great relevance for developing countries, where such dialytic methods are more often utilized, and serum analysis of vancomycin for the adjustment of the drug is not always available.

Author Contributions: Conceptualization, F.M.d.F. and D.P.; Methodology, F.M.d.F. and D.P.; Formal analysis, F.M.d.F., W.Z. and P.F.d.R.; Resources, A.L.B. and D.P.; Data curation, F.M.d.F. and D.P.; Writing—original draft preparation, F.M.d.F. and W.Z.; Writing—review and editing, A.L.B. and D.P.; Supervision, A.L.B. and D.P.; Funding acquisition: D.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), grant number 2017/02311-4 and The APC was funded by Pró Reitoria de Pós Graduação—UNESP.

Conflicts of Interest: The authors declare there is no conflict of interest.

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