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TESE

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EFEITOS DE DIURÉTICOS TIAZÍDICOS E DE DIFERENTES DOSES DE DIURÉTICO POUPADOR DE POTÁSSIO SOBRE PRESSÃO ARTERIAL, PARÂMETROS BIOQUÍMICOS E INCIDÊNCIA DE EFEITOS ADVERSOS EM PACIENTES COM HIPERTENSÃO ARTERIAL

Porto Alegre

2025

Leonardo Grabinski Bottino

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Tese apresentada ao Programa de Pós-Graduação em Cardiologia e Ciências Cardiovasculares da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Doutor em Cardiologia.

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Dedico este trabalho à minha família,
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LISTA DE ABREVIATURAS E SIGLAS

ABPM – Monitorização Ambulatorial da Pressão Arterial

ACE – Enzima Conversora de Angiotensina

ALLHAT – Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

BP – Blood Pressure (Pressão Arterial)

CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CTD – Clortalidona

CVD – Doença Cardiovascular

FIPE – Fundo de Incentivo à Pesquisa e Eventos

HCT – Hidroclorotiazida

MAPA – Monitorização Ambulatorial da Pressão Arterial

NCD-RisC – Non-communicable Diseases Risk Factor Collaboration

PA – Pressão Arterial

SHEP – Systolic Hypertension in the Elderly Program

SPRINT – Systolic Blood Pressure Intervention Trial

WHO – World Health Organization (Organização Mundial da Saúde)

1. RESUMO

O presente estudo teve como objetivo comparar os efeitos de diuréticos tiazídicos (clortalidona 25 mg e hidroclorotiazida 50 mg) e diferentes doses de amilorida (5 mg e 10 mg) sobre a pressão arterial (PA), aferida por monitorização ambulatorial da pressão arterial (MAPA), parâmetros bioquímicos e incidência de efeitos adversos em pacientes com hipertensão arterial. Em um ensaio clínico randomizado, duplo-cego, com delineamento fatorial, 85 pacientes foram randomizados e acompanhados por 12 semanas. Não houve interação entre os tratamentos, permitindo análises separadas. Os resultados demonstraram que clortalidona e hidroclorotiazida apresentaram efeitos semelhantes na redução da PA sistólica e diastólica, tanto em medidas de consultório quanto por MAPA, com deltas entre grupos de -1,1 mmHg (-8,0 a 5,9, P = 0,8) para PA sistólica de 24 horas e -2,3 mmHg (-10,3 a 5,7, P = 0,6) para PA noturna. Não houve diferenças significativas nos parâmetros bioquímicos entre os tratamentos. As doses de 5 mg e 10 mg de amilorida apresentaram efeitos semelhantes sobre a PA e parâmetros bioquímicos, antagonizando eficazmente a hipocalemia e o aumento de glicemia induzidos pelos diuréticos tiazídicos. Efeitos adversos, como cãibras musculares, foram infrequentes e distribuídos igualmente entre os grupos. Este estudo fornece evidências robustas de que clortalidona e hidroclorotiazida, na proporção de dose 1:2, são equivalentes em eficácia e segurança, e que a amilorida, em doses de 5 e 10 mg, é eficaz na prevenção de efeitos adversos metabólicos, com efeito hipotensor fraco ou inexistente. Palavras-chave: hipertensão arterial; clortalidona; hidroclorotiazida; amilorida; monitorização ambulatorial da pressão arterial.

1. ABSTRACT

This study aimed to compare the effects of thiazide diuretics (chlorthalidone 25 mg and hydrochlorothiazide 50 mg) and different doses of amiloride (5 mg and 10 mg) on blood pressure (BP), measured by ambulatory blood pressure monitoring (ABPM), biochemical parameters, and the incidence of adverse effects in patients with arterial hypertension. In a factorial, double-blind, randomized clinical trial, 85 patients were randomized and followed for 12 weeks. No interaction was observed between treatments, allowing separate analyses. The results showed that chlorthalidone and hydrochlorothiazide had similar effects on systolic and diastolic BP reduction, both in office measurements and by ABPM, with between-group deltas of -1.1 mmHg (-8.0 to 5.9, P = 0.8) for 24-hour systolic BP and -2.3 mmHg (-10.3 to 5.7, P =

0.6) for nighttime BP. No significant differences were observed in biochemical parameters between treatments. Amiloride at doses of 5 mg and 10 mg showed similar effects on BP and biochemical parameters, effectively antagonizing hypokalemia and increased glycemia induced by thiazide diuretics. Adverse effects, such as muscle cramps, were infrequent and evenly distributed among groups. This study provides robust evidence that chlorthalidone and hydrochlorothiazide, at a 1:2 dosing ratio, are equivalent in efficacy and safety, and that amiloride, at doses of 5 and 10 mg, is effective in preventing metabolic adverse effects, with a weak or negligible BP-lowering effect.

Keywords: arterial hypertension; chlorthalidone; hydrochlorothiazide; amiloride; ambulatory blood pressure monitoring.

2. BASE TEÓRICA

Riscos de pressão arterial elevada

Hipertensão arterial sistêmica (HAS) é a principal causa de doenças cardiovasculares. Estudos de coorte, iniciando-se com o clássico estudo de Keith, Wagener e Barker, demonstraram que a elevação da pressão arterial se associa com maior probabilidade de ocorrência de doenças cardiovasculares [1]. Metanálise dessas coortes realizada pelo “Prospective collaboration”, com mais de 1 milhão de indivíduos seguidos por pelo menos 15 anos, demonstrou que o risco de morte por doença arterial coronariana e por acidente vascular encefálico aumenta progressivamente a partir de 75 mmHg e 115 mmHg de PA diastólica e sistólica, respectivamente, dobrando o risco a cada aumento de 10 mmHg de PA diastólica e a cada 20 mmHg de PA sistólica [2]. A pressão arterial aumentada também é, conforme diversos estudos observacionais, a causa principal ou importante causa de consequências a longo prazo como insuficiência cardíaca, fibrilação atrial doença renal crônica, doença arterial periférica, síndromes aórticas, demência, doença de Alzheimer, disfunção erétil, entre outras [3].

Prevalência de hipertensão arterial e estimativas de controle

A maioria dos estudos de prevalência em hipertensão utilizaram critérios conservadores para definir o diagnóstico. Colaboração entre centenas de pesquisadores sobre hipertensão arterial e outros fatores de risco cardiovasculares - Non-communicable Diseases Risk Factor Collaboration (NCD-RisC) – tem feito inúmeras meta-análises de dados individuais, que chegam em alguns estudos a mais de 100 milhões de participantes. Em publicação de 2021 [4], empregando PA $\geq$140/90 mmHg como critério diagnóstico, demonstraram que a o número absoluto de pessoas com hipertensão passou de 331 milhões de mulheres e 317 milhões de homens em 1990 para 626 e 652 milhões em 2019, apesar das taxas de prevalência não terem se modificado. As taxas de PA controlada são de somente de um indivíduo entre cinco com o diagnóstico de hipertensão [4].

Com o emprego de critérios diagnósticos mais estritos, propostos pela última diretriz das sociedades de Cardiologia dos Estados Unidos (130/80 mmHg), 63% de adultos com 45 a 75 anos nos Estados Unidos e 55% na China são hipertensos [5].

Meta-análise de estudos de prevalência no Brasil demonstrou que a prevalência de hipertensão entre adultos era de 28.7% (95% CI 26.2–31.4). Análise restrita a indivíduos idosos evidenciou prevalência de 68.0% (95% CI 65.1–69.4) [6, 7].

Reversão do risco decorrente de PA elevada

Ensaios clínicos randomizados e metanálises com centenas de milhares de participantes demonstraram haver reversão do risco cardiovascular evidenciado pelo Prospective Collaboration [3]. Para uma redução de 5, 10, 20 e 40 mmHg estima-se uma redução de incidência de eventos cardiovasculares 12,5, 25, 50 e 75% na incidência de doença cardiovascular. Nas meta-análises a redução de risco observada para aqueles valores de redução da PA foi de 7, 17, 22, 54, e 64%, respectivamente, demonstrando-se experimentalmente que a elevação da PA é a causa maior das doenças cardiovasculares [8].

A evidência matemática sustenta a necessidade de prevenir a elevação da PA com a idade e de reverter valores elevados em pessoas com hipertensão arterial. Medidas não medicamentosas têm, em geral, baixa efetividade. Exceção importante é o efeito redutor da PA e de prevenção de eventos cardiovasculares com a substituição de parte do cloreto de sódio utilizado como condimento por cloreto de potássio [9]. A reversão do risco cardiovascular nesse estudo se deu também na proporção esperada pela redução da PA.

Escolha de agentes anti-hipertensivos

Os objetivos do tratamento anti-hipertensivo devem ser orientados por alvos terapêuticos. O ensaio clínico SPRINT testou a estratégia de reduzir a PA sistólica a valores inferiores a 120 mmHg, comparativamente a 140 mmHg [10]. Houve redução relativa de 27% em mortes por qualquer causa com o tratamento mais intensivo. Resultados positivos mas menos intensos foram observados no estudo ESPRIT [11], que incluiu pacientes com diabetes ou com história de AVC, excluídos do estudo SPRINT. O ensaio clínico randomizado BPROAD demonstrou benefício similar em pacientes com diabetes [12]. Novo ensaio clínico randomizado em pacientes com diabetes e desenho experimental similar, o estudo OPTIMAL-diabetes, está próximo do encerramento no Brasil, juntamente com o estudo OPTIMAL-stroke, realizado em pacientes com história de AVC.

A escolha de agentes anti-hipertensivos tem importância por sua capacidade de reduzir a pressão arterial, e por consequência de eventos cardiovasculares, com perfil de risco aceitáveis. Diuréticos se destacam nestes aspectos.

Diuréticos

Duas questões serão abordadas nesta tese, reportando os resultados de um ensaio clínico randomizado: efeitos sobre a pressão arterial e efeitos adversos de clortalidona e hidroclorotiazida e o potencial efeito aditivo de diferentes doses de amilorida para a redução da PA e para prevenir efeitos adversos de clortalidona e hidroclorotiazida. O protocolo do ensaio clínico foi publicado anteriormente [13].

Efetividade na redução de eventos cardiovasculares

A descoberta de diuréticos inclui-se entre os avanços seminais no tratamento e prevenção de doenças. Em revisão recente [14] revisamos a farmacologia e a efetividade clínica de diuréticos antigos, novos e novas evidências de eficácia dos antigos. Abordamos seus efeitos em insuficiência cardíaca, doença renal crônica e hipertensão arterial, onde diuréticos têm particular efetividade.

Os diuréticos tiazídicos foram descobertos na década de 1950, sendo inicialmente utilizado em pacientes com insuficiência cardíaca e doença renal crônica. Um estudo histórico demonstrou o efeito da clorotiazida no manejo da hipertensão [15]. Posteriormente outros tiazídicos e similares a tiazídicos ("*thiazide-like diuretics*") foram incorporados, sendo os de maior emprego hoje hidroclorotiazida, clortalidona e indapamida.

Diversos estudos randomizados com tais drogas demonstraram a redução de desfechos cardiovasculares em comparação com placebo, como os clássicos Veterans de 1967 e 1970 [16, 17], em que a hidroclorotiazida foi componente do tratamento triplo, demonstrando importante redução desfechos cardiovasculares com tal droga no tratamento da hipertensão diastólica.
Em 1991, foi publicado outro o estudo Systolic Hypertension in the Elderly Program (SHEP), em que o tratamento da hipertensão arterial sistólica isolada baseado em clortalidona promoveu significativa redução de eventos cardiovasculares em idosos com hipertensão sistólica isolada

[18]. Esse estudo caracterizou hipertensão sistólica isolada como doença. O primeiro estudo a demonstrar redução de mortalidade, além de desfechos cardiovasculares, foi o HYVET [19], com tratamento baseado em indapamida em pacientes com mais de 80 anos. O PROGRESS foi outro estudo relevante, por demonstrar que o tratamento baseado em indapamida reduziu em 40% a recorrência de AVC e outros eventos cardiovasculares em pacientes com história de AVC [20].

Em meta-análise de ensaios clínicos em que se compararam diversas classes de anti-hipertensivos em sua capacidade de reduzir eventos cardiovasculares comparativamente a placebo houve superioridade de diuréticos sobre outros agentes [21]. Destaca-se nessa meta-análise a menor efetividade dos bloqueadores do receptor da angiotensina, medicamentos anti-hipertensivos usados preferencialmente em muitos países. Diversas revisões descritivas sobre o tema apontam a baixa efetividade desses medicamentos na prevenção de eventos cardiovasculares, incluindo uma publicada mais recentemente [22].

O estudo Antihypertensive and Lipid Lowering to Treat Heart Attack Trial (ALLHAT) randomizou mais de 40.000 participantes para o uso de clortalidona, anlodipino, lisinopril e doxazosina [23]. O braço do estudo com doxazosina foi interrompido precocemente pela maior incidência de eventos cardiovasculares. A incidência de IAM - fatal ou não fatal - foi similar entre as três drogas restantes do estudo. Clortalidona foi superior a anlodipino para a prevenção de insuficiência cardíaca e a lisinopril para a prevenção de 10% eventos cardiovasculares, AVC e insuficiência cardíaca.

Efetividade na redução da PA e efeitos adversos

Entre estudos de maior porte e duração comparando efeitos anti-hipertensivos e efeitos adversos de anti-hipertensivos destaca-se o estudo TOHMS [24] e o estudo PREVER-tratamento [25]. No primeiro compararam-se cinco classes de anti-hipertensivos e placebo, demonstrando-se equivalência entre os fármacos quanto à redução da PA. Clortalidona foi mais eficaz em reduzir a massa de ventrículo esquerdo. No estudo PREVER-tratamento, participantes tratados primariamente com a associação de clortalidona e amilorida tiveram redução de PA superior ao grupo tratado com losartana, a despeito do segundo grupo ter recebido maior número de fármacos anti-hipertensivos suplementares.

Comparação entre hidroclorotiazida e clortalidona

A diferença farmacológica entre clortalidona e hidroclorotiazida é estudada há muitas décadas; estima-se que a clortalidona seja mais potente cerca de 1,5 a 2x em relação à hidroclorotiazida, e que há uma diferença farmacocinética relevante, com a meia-vida de eliminação da clortalidona sendo estimada em cerca de 50h e da hidroclorotiazida em 6h [26]. Há poucos ensaios clínicos randomizados comparando o efeito anti-hipertensivo e efeitos adversos entre hidroclorotiazida e clortalidona e somente um estudo com desfechos cardiovasculares.

A comparação entre clortalidona e hidroclorotiazida inicia-se com um ensaio clínico cruzado com monitorização ambulatorial da PA (MAPA) em 24 pacientes [27]. Em doses presumivelmente equivalentes (12,5 e 25 mg de clortalidona para 25 e 50 mg de hidroclorotiazida), com duplicação da dose no cruzamento, houve superioridade de clortalidona na redução da PA. Uma revisão sistemática identificou somente mais dois estudos que compararam clortalidona com hidroclorotiazida, mas os fármacos foram usados em associação com outros fármacos e os estudos tinham pequenas amostras [28]. Ensaio clínico publicado posteriormente [29] avaliou o efeito hipotensor por MAPA de doses baixas e presumivelmente equivalentes de clortalidona (6,25 mg) e hidroclorotiazida (12,5 mg), em apresentação usual e de liberação retardada. Os efeitos foram equivalentes entre clortalidona e a apresentação de liberação retardada de hidroclorotiazida, mas não de hidroclorotiazida em apresentação usual. Em ensaio clínico em que hidroclorotiazida ou clortalidona foram adicionadas na mesma dose azilsartano [30] houve superioridade de clortalidona.

Na época do planejamento deste estudo havia inequívoca lacuna na demonstração do efeito hipotensor de diferentes doses dos diuréticos em estudo. Na prática clínica utilizava-se mais comumente hidroclorotiazida, apesar de se sugerir que clortalidona fosse mais eficaz [31]. Muitos entendiam que fossem fármacos equipotentes [31]. Nesse cenário foi desenhado o ensaio clínico randomizado apresentado nesta tese, que tem como um dos objetivos comparar o efeito hipotensor e efeitos adversos de clortalidona e hidroclorotiazida em doses presumivelmente equivalentes.

Em 2022 foram publicados os resultados de um ensaio clínico randomizado comparando o efeito de hidroclorotiazida nas doses de 25 e 50 mg com clortalidona nas doses de 12,5 e 25 mg na prevenção de desfechos cardiovasculares [32]. A incidência de um desfecho cardiovascular

composto foi de 10,4% no grupo que recebeu clortalidona e de 10,0% nos tratados com hidroclorotiazida. Hipocalemia ocorreu em 6,0% nos tratados com clortalidona e de 4,4% nos tratados com hidroclorotiazida. Um erro sistemático pode ter enviesado os resultados, pois a alocação aos tratamentos foi feita de forma aleatória em pacientes em tratamento com os diuréticos, sendo a grande maioria (94,5%) usuária de hidroclorotiazida. A possibilidade de serem pacientes já adaptados ao emprego de hidroclorotiazida, incluindo controle prévio de hipopotassemia, não pode ser excluída, mas é pouco provável que os efeitos primordiais tenham sido influenciados.

Comparação entre diferentes doses de amilorida

Diuréticos tiazídicos podem ocasionar efeitos metabólicos adversos, como hipocalemia, hiponatremia, hiperuricemia, hiperglicemia, hiperlipidemia e hipomagnesemia. O mais importante é a hipocalemia, que tem como consequência perda de efetividade na prevenção de doença cardiovascular e aumento da glicemia. No clássico ensaio clínico “Systolic Hypertension in the Elderly Program – SHEP [33] perdeu-se a eficácia de tratamento baseado em clortalidona para a prevenção de desfechos cardiovasculares em participantes com queda de potássio abaixo de 3,5 meq/l.

A suplementação de potássio associa-se com redução de PA em pacientes hipertensos [34]. Dietas com substituição de parte do cloreto de sódio por cloreto de potássio associam-se com redução da PA [35] e prevenção de eventos cardiovasculares [36].

Diuréticos poupadores de potássio, como amilorida e triantereno, inibidores do canal de sódio epitelial, são usados há décadas, mas não têm uso difundido na prática clínica. Agentes de outros grupos farmacológicos, como inibidores da ECA e bloqueadores de receptores de angiotensina também poupam potássio, sendo mais utilizados na prática clínica. Há poucos estudos comparativos entre diuréticos poupadores de potássio e antagonistas do sistema renina-angiotensina. Ensaio clínico randomizado com pacientes hipertensos em uso de hidroclorotiazida demonstrou elevação de 0,3 meq/l com o tratamento com amilorida (2,5–5 mg/dia) e enalapril (10–20 mg/dia) [37].

Estudos observacionais e ensaios clínicos randomizados subsidiam o benefício de associar esses diuréticos poupadores de potássio ao tratamento com diuréticos tiazídicos. Antigo estudo de

casos e controles identificou que participantes que utilizavam poupadores de potássio tiveram menor taxa de morte súbita do que os que usavam diuréticos tiazídicos isolados [38]. Em dois ensaios clínicos randomizados de grande porte a associação de diurético tiazídico com amilorida promoveu redução de eventos cardiovasculares. O estudo MRC of Elderly Patients demonstrou a superioridade da associação sobre placebo e atenolol [39]. No estudo INSIGHT [40] a associação foi superior a uma apresentação de nifedipino de liberação retardada para a prevenção de infarto do miocárdio e insuficiência cardíaca.

Uma questão em aberto é se a amilorida e outros poupadores de potássio têm efeito hipotensor. O estudo Pathway-3 demonstrou efeito similar de hidroclorotiazida (12,5 a 25 mg) e amilorida (10 a 20 mg) sobre a PA [41]. A associação entre ambos promoveu diminuição adicional de PA. Meta-análise de dados agregados com somente 496 participantes não identificou efeito hipotensor de amilorida e triantereno em baixas doses [42]. Em meta-análise em rede que incluiu 276 ensaios clínicos randomizados duplo-cegos, com 58 807 participantes, identificou-se que a associação com diuréticos poupadores de potássio aumentou o efeito hipotensor de diuréticos tiazídicos [43]. A diferença entre os estudos pode se dever ao maior número de observações na meta-análise em rede, que também incluiu outros poupadores de potássio, como antagonistas de aldosterona.

A redução de níveis séricos de potássio por diuréticos tiazídicos associa-se com o aumento da glicemia [44]. O estudo Pathway-3 [41] demonstrou que amilorida, em doses de 10 a 20 mg, antagonizou a queda dos níveis séricos de potássio promovida por hidroclorotiazida (12.5 a 25 mg) e o aumento da glicemia. Na meta-análise em rede citada acima [43], o aumento de glicose gerado pelos tiazídicos em monoterapia foi atenuado com o uso de poupadores de potássio.

Os ensaios clínicos PREVER-prevenção [45] e PREVER-tratamento [26] utilizaram proporção menor de amilorida em relação a clortalidona, 2,5 mg de amilorida para 12,5 mg de clortalidona no primeiro e esta proporção no segundo, que podia ser dobrada para 5 mg de amilorida e 25 mg de clortalidona. O potássio sérico ao fim de 18 meses de tratamento foi praticamente igual no PREVER-prevenção (4,4 meq/l no grupo ativo versus 4,5 meq/l no grupo placebo). No PREVER-tratamento o potássio sérico caiu a 4,2 meq/l no grupo tratado com clortalidona/amilorida, comparativamente a 4,5 meq/l no grupo tratado com losartana.

3. JUSTIFICATIVA

Ainda não é bem definido na literatura a equivalência ou não entre diferentes diuréticos tiazídicos, sobretudo em relação a PA aferida por MAPA. Portanto, justifica-se o presente estudo para melhor compreensão do tema com dados prospectivos e randomizados a equivalência entre as doses de diferentes diuréticos tiazídicos (clortalidona e hidroclorotiazida) em relação ao efeito em PA, parâmetros metabólico e efeitos adversos.

Também se justifica o estudo em relação à comparação entre as diferentes doses de diurético poupador de potássio (em questão a amilorida) em associação com tiazídicos; há a questão na literatura se possuem efeito anti-hipertensivo por si, qual o grau de proteção em relação a efeitos adversos dos tiazídicos e se há diferença entre diferentes doses de amilorida.

4. OBJETIVOS

4.1 Comparar o efeito de clortalidona na dose de 25 mg com 50 mg de hidroclorotiazida sobre a pressão arterial aferida por MAPA, parâmetros bioquímicos e efeitos adversos em pacientes com hipertensão arterial.

4.2 Comparar o efeito de amilorida na dose de 5 mg e na dose de 10 mg sobre a pressão arterial aferida por MAPA, parâmetros bioquímicos e efeitos adversos em pacientes com hipertensão arterial e tratados simultaneamente com clortalidona na dose de 25 mg ou hidroclorotiazida.

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6. ARTIGO PRINCIPAL

COMPARATIVE EFFECTIVENESS OF CTD VERSUS HCT AND HIGHER AND LOWER DOSES OF AMILORIDE ON BLOOD PRESSURE AND BIOCHEMICAL PARAMETERS.

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ABSTRACT

Diuretics are used as the primary option or in combination with other medications to reduce the risk of high blood pressure (BP). The dosing ratio between hydrochlorothiazide and chlorthalidone for lowering BP, as well as the effects of different amiloride doses on BP and antagonizing the thiazide's adverse effects, remain unclear. In a factorial, double-blind randomized clinical trial, we compared the effects of chlorthalidone 25 mg with hydrochlorothiazide 50 mg and amiloride 5 mg and 10 mg on BP, measured by ABPM, and on laboratory parameters. A total of 85 patients were randomized and followed for 12 weeks. The treatments showed no interaction, and comparisons were thus assessed separately. Hydrochlorothiazide and chlorthalidone had nearly identical effects on systolic and diastolic BP measured at the office and by ABPM. The between-group deltas (hydrochlorothiazide minus chlorthalidone) of systolic 24-hour and nighttime BP were -1.1 (-8.0 to 5.9), P = 0.8, and -2.3 (-10.3 to 5.7), P = 0.6, respectively. The effects on laboratory parameters did not differ between treatments. The effects of amiloride 5 mg and 10 mg on BP and laboratory parameters were also not distinct. This study provides robust evidence that chlorthalidone and hydrochlorothiazide, in a dosing ratio of 1:2, have similar effects on blood pressure and laboratory parameters. Amiloride, at doses of 5 and 10 mg, effectively antagonized the hypokalemia and increase in serum glucose induced by chlorthalidone and hydrochlorothiazide, and exhibited similar effects on blood pressure, suggesting that amiloride has, at best, a weak blood pressure-lowering effect.

INTRODUCTION

High blood pressure is the primary cause of cardiovascular diseases [1]. Effective treatment to lower blood pressure is essential to reduce the global burden of disease related to high BP [2, 3]. Treatments targeting lower BP levels have demonstrated an almost exact reversal of high BP risks estimated in cohort studies [4].

Drug treatment aimed at a rapid escalation of associations to lower BP has been advocated [5, 6]. Drugs that align a higher BP-lowering effect with tolerable adverse effects should be preferred, including the early association of drugs [7, 8]. Diuretics have the best records in terms of cardiovascular disease prevention, serving as the cornerstone drug in seminal studies [9-13]. A meta-analysis comparing all classes of BP-lowering drugs with placebo showed the relative superiority of diuretics [14]. Among studies comparing the BP-lowering efficacy of drugs, the PREVER-treatment study demonstrated a clinically relevant superiority of a treatment based on the association of CTD with amiloride compared with a treatment based on losartan [15], which explains the lower effectiveness of ARBs in the prevention of CVD [16].

Chlorthalidone (CTD), indapamide, and hydrochlorothiazide (HCT) were the diuretics most frequently used in large clinical trials. At the time of planning this trial [17], there was weak evidence regarding the comparative BP-lowering effectiveness of these diuretics. The equivalence of equipotent doses of CTD and HCT, in a ratio of 1:0 to 1.7 (18), was suggested but not tested in a head-to-head trial [17]. One of the objectives of this study was to compare the equivalence of doses of CTD and HCT that were presumably equivalent [18]. In the meantime, a randomized controlled trial demonstrated the equivalence of CTD at doses of 12.5 mg and 25 mg with HCT at doses of 25 mg and 50 mg in the prevention of cardiovascular events [19].

Hypokalemia and hyperglycemia are common adverse effects of thiazide diuretics, and evidence suggests that the former causes the latter [20]. The use of potassium-sparing diuretics prevents the decrease in serum potassium levels and, consequently, the increase in glycemia [21]. It remains unclear which doses of amiloride antagonize the biochemical effects of thiazides. In the PREVER-prevention [22] and treatment trial [15], a ratio of 5 (2,5 mg and 5 mg of amiloride for 12.5 and 25 mg of CTD) proved insufficient to prevent the drop in serum potassium levels. Another open question is whether amiloride has its own BP-lowering effect [23-25]. These questions were explored in this randomized factorial clinical trial.

METHODS

This study was registered on ClinicalTrials.gov under NCT03928145, and a detailed protocol description has been published elsewhere [17].

Inclusion criteria include individuals aged 30 to 75 years who are not using BP-lowering drugs and have a mean 24-hour systolic ambulatory BP ≥130 mmHg or a mean 24-hour diastolic BP ≥80 mmHg. Criteria for exclusion include low life expectancy, cardiovascular disease (heart failure, previous myocardial infarction, or stroke), secondary hypertension, systolic office BP ≥160 mmHg or diastolic BP ≥100 mmHg, as well as pregnancy or prospective pregnancy during the study.

Interventions: the trial features a factorial design with simultaneous interventions: a thiazide diuretic (CTD 25 mg or HCTZ 50 mg) and a potassium-sparing diuretic (amiloride 5 mg or amiloride 10 mg). Participants will be randomly assigned to four parallel groups: CTD 25 mg + amiloride 5 mg, CTD 25 mg + amiloride 10 mg, HCT 25 mg + amiloride 5 mg, and HCTZ 50 mg + amiloride 10 mg. In the original protocol, the dosages of amiloride were to be 10 and 20 mg, respectively. A report of a serious adverse effect, hyperkalemia in a participant using 20 mg of amiloride, led to the interruption of randomization and the modification of the dosages of amiloride to 5 and 10 mg. The thiazide diuretics and amiloride were combined in a single capsule, taken in the morning upon waking. Adherence to trial medication was assessed through pill counts.

The primary outcomes were the differences between the treatment arms in the mean change from baseline in 24-hour systolic and diastolic BP measured by ambulatory blood pressure monitoring (ABPM) at 12 weeks. ABPM was performed using portable monitors (Spacelabs 90207, Redmond, WA, USA). The secondary outcomes included: the differences between the treatment arms in mean change from baseline to 12 weeks in daytime and nighttime systolic and diastolic BP; systolic and diastolic BP measured by office BP; laboratory parameters; the differences between treatment arms in the proportion of participants reporting adverse events; and the differences between treatment arms in the proportion of participants achieving BP control at 12 weeks. BP control was defined as <140/90 mmHg for office BP and <130/80 mmHg for 24-hour ABPM.

After confirmation of ABP and other eligibility criteria, participants were randomized at visit 1, alongside anthropometric, clinical, and laboratory assessments. Participants were seen in week 6 for office BP measurements (averaging 3 readings), evaluation of treatment adherence, investigation of adverse events, and delivery of study medication. In the final visit during week 12, ABPM, clinical, and laboratory tests were performed.

A computer-generated sequence created by the Random Allocation Software was used to randomly assign patients to the four interventions, stratified by 24-hour systolic on ABPM (<140 or ≥140 mmHg), with a 1:1:1:1 allocation using random block sizes to generate an equal allocation ratio and parallel groups. An independent researcher not involved in the enrollment will produce the randomization sequence. The research team was blinded to the randomization sequence.

Statistical methods

Sample size calculation: For an absolute difference of 6 mmHg in systolic BP on 24-h ABPM, with an alpha of 0.05, power of 80%, and a standard deviation of 9 mmHg, the sample size was 76 participants. The sample size was increased by 10% to account for potential losses in follow-up.

All data were analyzed according to the intention-to-treat principle, considering all patients as randomized, regardless of whether they received the randomized treatment. Analyses were performed using SPSS for Windows (version 17; SPSS Inc., Chicago, Illinois, USA). A P value <0.05 was considered statistically significant.

The BP levels among treatment groups at each visit were compared using a t-test for independent samples, and a random-effects linear model fitted for systolic and diastolic BP was utilized to compare BP by treatment group during follow-up. The random-effects model includes an intercept and a slope to adjust for within-participant correlation among the longitudinal data, including a test for interaction. Without interaction between the treatments, the analysis would compare the effects of CTD with HCT and amiloride at low and high doses. Otherwise, the comparison would be made between the four cells (CTD plus amiloride 5, CTD and amiloride 10, HCT 25 and amiloride 5, and HCT 25 and amiloride 10).

The participants were informed about the study's objectives and the risks of participation and provided written consent.

RESULTS

A total of 85 participants were randomized. Fifteen individuals randomized at the beginning of the COVID pandemic could not follow the protocol and did not return for a final evaluation, resulting in a final sample of 70 participants. We conducted an analysis to test the effect of both treatments on the primary objective, which showed no difference or trend of difference between the treatments. Therefore, we present the results without further enrollment of patients due to the likely futility of studying more individuals. A comparison between the baseline data of the participants and those not included in the analysis showed no differences. There was no interaction between the treatments in systolic ABP (P = 0.99), and the data were analyzed separately for CTD and HCT, as well as for high and low doses of amiloride.

Figure 1. Flow chart of the study

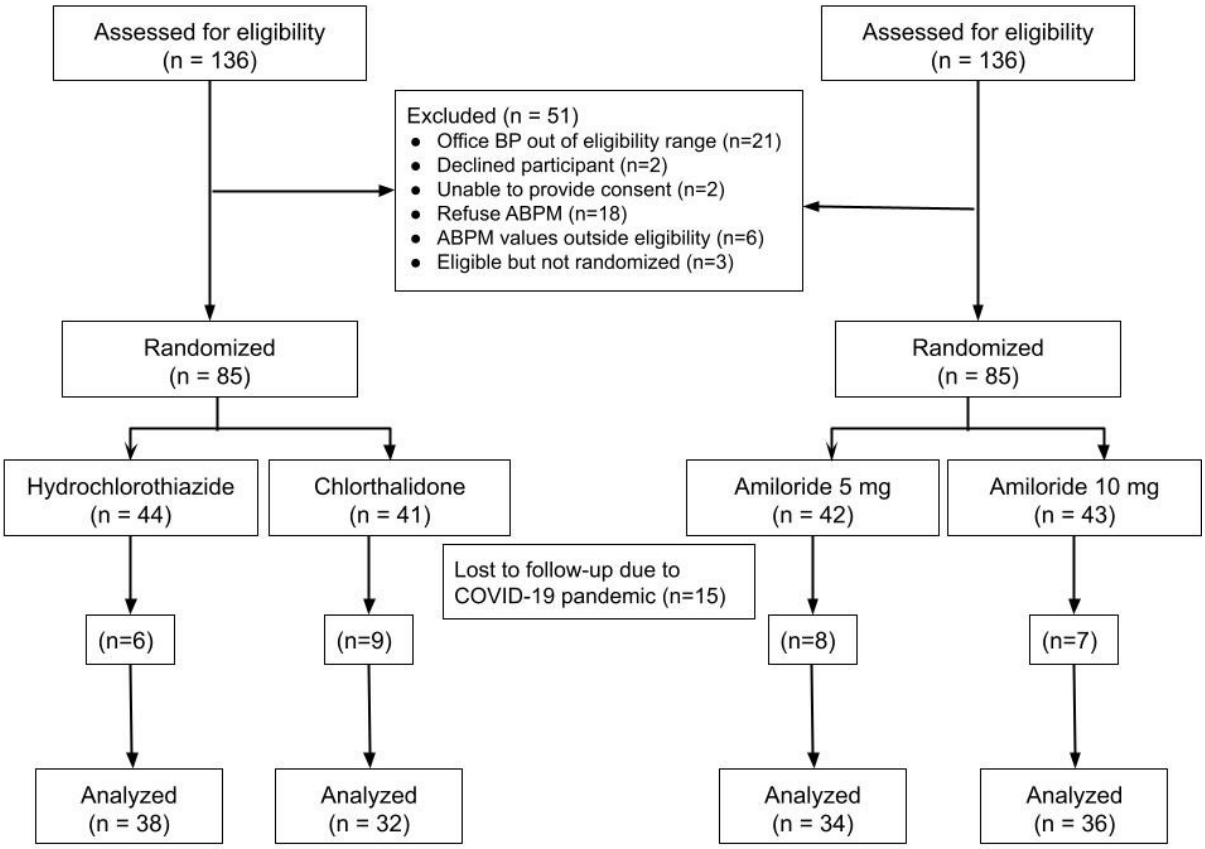


Table 1 shows that the baseline characteristics of the participants did not differ substantially by treatment.

Table 1. Characteristics of participants at baseline according to the intervention groups

	HCT 50 (n=38)	CTD 25 (n=32)	Amiloride 5 (n=34)	Amiloride 10 (n=36)
Age (years)	59.8 ± 8.1	58.8 ± 8.5	59.0 ± 8.8	59.7 ± 7.7
Male gender	15 (53.6)	13 (46.4)	16 (57.1)	12 (42.9)
Years at school	11.4 ± 4.5	11.9 ± 3.0	10.4 ± 3.3	12.8 ± 4.1
Current smoking	6 (66.7)	3 (33.3)	6 (66.7)	3 (33.3)
Body mass index (kg/m^2)	28.3 ± 3.9	29.4 ± 5.1	28.4 ± 5.1	29.1 ± 3.9
Office Systolic BP (mmHg)	134.0 ± 9.2	136.7 ± 9.9	136.6 ± 10.0	134.0 ± 9.0
Office Diastolic BP (mmHg)	81.3 ± 8.6	81.8 ± 9.5	82.0 ± 9.5	81.1 ± 8.5
Diabetes mellitus	6 (40.0)	9 (60.0)	9 (60.0)	6 (40.0)
Creatinine (mg/dL)	0.82 ± 0.14	0.83 ± 0.13	0.83 ± 0.143	0.82 ± 0.14
Sodium (mg/dL)	141.2 ± 1.8	140.9 ± 1.9	140.7 ± 1.7	141.3 ± 2.0
Potassium (mg/dL)	4.6 ± 0.4	4.6 ± 0.2	4.6 ± 0.4	4.6 ± 0.4
Urea (mg/dL)	31.2 ± 7.1	30.4 ± 6.7	31.3 ± 7.3	30.3 ± 6.5
Triglycerides (mg/dL)	132.0 ± 90.9	137.1 ± 103.8	142.2 ± 99.6	126.8 ± 94.1
Glucose (mg/dL)	101.9 ± 41.1	113.4 ± 46.1	118.3 ± 59.1	96.5 ± 12.6
HbA1c (%)	5.7 ± 0.9	6.2 ± 1.8	6.2 ± 1.8	5.7 ± 0.8
Total Cholesterol (mg/dL)	201.7 ± 43.2	203.9 ± 45.5	192.3 ± 46.8	212.9 ± 39.2
LDL Cholesterol (mg/dL)	124.8 ± 38.4	130.6 ± 34.6	116.9 ± 40.5	137.8 ± 29.2

Table 2 indicates no difference in the effects of CTD 25 mg and HCT 50 mg on BP measured in the office or during periods of ABP monitoring.

Table 2. Office and ambulatory blood pressure before and after Hydrochlorothiazide and Chlorthalidone [Mean ±SD]

Blood pressure (mmHg)	Hydrochlorothiazide (n=38)		Within group delta	Chlorthalidone (n=32)		Within group delta	Between groups delta (95% CI)	P value
	Baseline	Follow-up		Baseline	Follow-up			
Office Systolic BP	134.1 ± 9.1	122.9 ± 9.8	11.2 ± 10.9	136.7 ± 9.9	125.5 ± 12.4	11.3 ± 13.1	-0.03 (-5.8 to 5.7)	1.0
Office Diastolic BP	81.7 ± 8.9	77.4 ± 7.4	4.4 ± 7.6	81.8 ± 9.5	76.7 ± 9.8	5.1 ± 8.5	-0.7 (-4.6 to 3.1)	0.7
24-hour Systolic BP	133.0 ± 9.9	121.5 ± 11.2	11.5 ± 11.7	133.2 ± 15.3	120.6 ± 12.5	12.6 ± 17.3	-1.1 (-8.0 to 5.9)	0.8
Daytime Systolic BP	136.8 ± 9.4	125.0 ± 9.8	11.8 ± 11.2	137.0 ± 16.0	123.9 ± 13.3	13.1 ± 17.4	-1.3 (-8.1 to 5.6)	0.7
Nighttime Systolic BP	124.4 ± 13.8	113.1 ± 16.8	11.2 ± 15.5	127.2 ± 15.3	113.7 ± 15.1	13.5 ± 18.2	-2.3 (-10.3 to 5.7)	0.6
24-hour Diastolic BP	81.6 ± 5.6	77.1 ± 5.6	4.6 ± 4.8	82.9 ± 11.2	75.9 ± 6.0	7.1 ± 11.1	-2.5 (-6.5 to 1.5)	0.2
Daytime Diastolic BP	84.2 ± 5.5	79.8 ± 5.3	4.4 ± 4.9	83.8 ± 7.3	78.3 ± 6.9	5.4 ± 6.7	-1.0 (-3.8 to 1.8)	0.5
Nighttime Diastolic BP	75.9 ± 6.7	71.2 ± 7.7	4.7 ± 6.5	76.1 ± 6.5	70.7 ± 5.9	5.4 ± 7.6	-0.7 (-4.0 to 2.7)	0.7

Similarly, Table 3 shows no difference in the effects of amiloride 5 mg and amiloride 10 mg on BP measured under those conditions.

Table 3. Office and ambulatory blood pressure monitoring before and after amiloride 5 mg and 10 mg [Mean ±SD]

Blood pressure (mmHg)	Amiloride 5 mg (n=34)		Within group delta#	Amiloride 10 mg (n=36)		Within group delta#	Between groups delta# (95% CI)	P value
	Baseline	Follow-up		Baseline	Follow-up			
Office Systolic BP	136.6 ± 10.0	124.0 ± 10.0	12.7 ± 10.8	134.1 ± 8.9	124.2 ± 12.1	9.9 ± 12.8	2.8 (-2.9 to 8.4)	0.3
Office Diastolic BP	82.0 ± 9.5	76.6 ± 7.7	5.4 ± 7.3	81.6 ± 8.8	77.5 ± 9.3	4.1 ± 8.5	1.3 (-2.5 to 5.1)	0.5
24-hour Systolic BP	134.9 ± 10.7	122.3 ± 11.8	12.6 ± 12.8	131.5 ± 14.1	120.0 ± 11.6	11.5 ± 15.9	1.1 (-5.8 to 8.0)	0.7
Daytime Systolic BP	138.0± 10.1	125.2 ± 10.4	12.8 ± 12.0	135.9 ± 14.9	123.9 ± 12.4	12.0 ± 16.3	0.8 (-6.1 to 7.7)	0.8
Nighttime Systolic BP	127.4 ± 15.5	116.0 ± 17.4	11.4 ± 17.6	124.0 ± 13.4	110.9 ± 14.2	13.1 ± 16.0	-1.6 (-9.6 to 6.4)	0.7
24-hour Diastolic BP	81.2 ± 6.2	76.9 ± 5.8	4.3 ± 5.5	83.2 ± 10.3	76.2 ± 5.9	7.0 ± 10.2	-2.7 (-6.7 to 1.3)	0.2
Daytime Diastolic BP	83.4 ± 6.4	79.1 ± 5.9	4.3 ± 5.6	84.6 ± 6.3	79.1 ± 6.3	5.5 ± 6.0	-1.2 (-4.0 to 1.5)	0.4
Nighttime Diastolic BP	76.2 ± 7.1	72.3 ± 6.9	3.9 ± 7.1	75.8 ± 6.1	69.7 ± 6.7	6.1 ± 6.8	-2.1 (-5.5 to 1.2)	0.2

Tables 4 and 5 depict the effects of CTD versus HCT and low versus high doses of amiloride on laboratory parameters, respectively. Except for a greater decrease in the serum sodium concentration with amiloride 10 mg compared to amiloride 5 mg, there were no other differences between the treatments.

Table 4. Effect of Hydrochlorothiazide and Chlorthalidone on laboratory parameters (Mean ±SD)

	Hydrochlorothiazide (n=38)		Within group delta	Chlorthalidone (n=32)		Within group delta	Between groups delta (95% CI)	P value
	Baseline	Follow-up		Baseline	Follow-up			
Sodium (mg/dL)	141.2 ± 1.8	140.4 ± 1.5	0.8 ± 1.9	140.8 ± 1.8	139.8 ± 1.9	1.0 ± 1.6	-0.15 (-1.0 to 0.7)	0.7
Potassium (mg/dL)	4.6 ± 0.4	4.5 ± 0.4	0.1 ± 0.4	4.6 ± 0.3	4.5 ± 0.4	0.1 ± 0.4	0.003 (-0.2 to 0.2)	0.9
Creatinine (mg/dL)	0.81 ± 0.14	0.88 ± 0.13	-0.06 ± 0.09	0.83 ± 0.13	0.92 ± 0.15	-0.10 ± 0.09	0.04 (-0.007 to 0.08)	0.09
Glucose (mg/dL)	101.5 ± 40.7	101.5 ± 23.2	-0.05 ± 21.6	113.6 ± 46.8	112.4 ± 45.6	1.2 ± 22.1	-1.2 (-11.8 to 9.3)	0.8
HbA1c (%)	5.7 ± 0.9	5.8 ± 0.9	-0.15 ± 0.4	6.3 ± 1.8	6.6 ± 1.8	-0.28 ± 0.6	0.1 (-0.1 to 0.4)	0.3
Total Cholesterol (mg/dL)	202.1 ± 42.7	206.6 ± 44.3	-4.6 ± 29.0	203.9 ± 45.5	219.1 ± 51.9	-15.2 ± 24.8	10.6 (-2.4 to 23.6)	0.11
LDL Cholesterol (mg/dL)	125.3 ± 38.0	130.9 ± 37.9	-5.6 ± 22.7	130.3± 35.1	140.5 ± 42.0	-10.3 ± 24.7	4.7 (-6.7 to 16.1)	0.4

Table 5. Effect of Amiloride 5 mg and 10 mg on laboratory parameters (Mean ±SD)

	Amiloride 5 mg (n=34)		Within group delta	Amiloride 10 mg (n=36)		Within group delta	Between groups delta (95% CI)	P value
	Baseline	Follow-up		Baseline	Follow-up			
Sodium (mg/dL)	140.7 ± 1.7	140.6 ± 1.8	0.2 ± 1.7	141.3 ± 1.9	139.7 ± 1.6	1.6 ± 1.7	-1.4 (-2.2 to -0.6)	0.001
Potassium (mg/dL)	4.6 ± 0.4	4.5 ± 0.5	0.1 ± 0.5	4.6 ± 0.4	4.5 ± 0.4	0.1 ± 0.4	-0.008 (-0.2 to 0.2)	0.9
Creatinine (mg/dL)	0.83 ± 0.13	0.92 ± 0.13	-0.09 ± 0.09	0.81 ± 0.13	0.87 ± 0.14	-0.06 ± 0.10	0.03 (-0.07 to 0.02)	0.2
Glucose (mg/dL)	118.6 ± 60.0	113.0 ± 45.3	5.6 ± 26.7	96.2 ± 12.6	100.4 ± 21.2	-4.2 ± 14.6	9.8 (-0.5 to 20.0)	0.06
HbA1c (%)	6.2 ± 1.8	6.4 ± 1.8	-0.2 ± 0.5	5.7 ± 8.2	5.9 ± 0.9	-0.2 ± 0.5	0.05 (-0.2 to 0.3)	0.7
Total Cholesterol (mg/dL)	192.3 ± 46.8	199.6 ± 49.7	-7.3 ± 27.1	212.9 ± 38.6	224.3 ± 43.6	-11.4± 28.0	4.0 (-9.2 to 17.2.0)	0.5
LDL Cholesterol (mg/dL)	116.9 ± 40.5	124.1± 44.4	-7.2 ± 22.4	137.9 ± 29.2	146.0 ± 31.8	-8.2 ± 25.0	1.0 (-10.4 to 12.4)	0.9

Adverse events were rare and evenly distributed across the experimental groups, with no serious incidents. The most frequent issue was muscle cramps, reported by 6 participants in the HCT group, 3 in the CTD group, 4 in the amiloride 5 mg group, and 6 in the amiloride 10 mg group.

DISCUSSION

This randomized controlled trial with a factorial design provided consistent evidence that chlorthalidone at 25 mg and hydrochlorothiazide 50 mg have the same effect on blood pressure measured at the office or by ABM. Their effect on laboratory parameters was also similar, with infrequent adverse complaints. Amiloride in 5 and 10 mg doses also had a similar effect on blood pressure and laboratory parameters. There was no interaction between the treatments.

A few head-to-head randomized controlled trials compared the BP-lowering effect of chlorthalidone and hydrochlorothiazide in different doses. In a crossover trial with BP measured by ABPM, the effect of chlorthalidone was higher than that of hydrochlorothiazide in a 1:2 dosing ratio [26]. A systematic review of three studies with small sample sizes and duration identified a trend for superiority of chlorthalidone over hydrochlorothiazide in a 1:2 dosing ratio. [27] Chlorthalidone at a dose of 6.25 mg was superior to hydrochlorothiazide at 12.5 mg in a study using ABPM but was similar to a controlled release of hydrochlorothiazide at the same dose. [28] In a randomized controlled trial, combining chlorthalidone and hydrochlorothiazide at the same dose with azilsartan demonstrated that chlorthalidone was superior to hydrochlorothiazide in reducing blood pressure. [20].

While our trial was collecting data, a pragmatic randomized controlled trial demonstrated that chlorthalidone and hydrochlorothiazide in a 1:2 dosing ratio were equivalent in preventing cardiovascular events. Hypokalemia was more frequent in patients treated with chlorthalidone (6.0% vs 4.4%) [19]. The unblinded design and the fact that more than 90% of patients were being treated with hydrochlorothiazide 25 mg and were switched to chlorthalidone 12.5 mg could introduce a systematic bias because the participants were adapted to the original treatment. The almost identical incidence of CV events and the large sample size make this possibility unlikely.

The results of our trial fill a gap in the understanding of the risks associated with high blood pressure (BP), the effect of treatment on BP, and the evidence that such treatment reduces the incidence of cardiovascular events. Two of the more effective drugs used in treatment, chlorthalidone and hydrochlorothiazide, at a dosing ratio of 1:2, are interchangeable. It remains essential that doctors do not assume equivalence between the same doses of these diuretics.

The use of thiazide diuretics is associated with several electrolyte and metabolic adverse events, including hypokalemia, hyponatremia, hypomagnesemia, hyperuricemia, hyperglycemia, and hyperlipidemia. Only hypokalemia may outweigh their benefits in preventing cardiovascular disease, as shown in participants of the Systolic Hypertension in the Elderly Program – SHEP study who experienced a drop in serum levels below 3,5 meq/l. [29]. The supplementation of

potassium lowers BP in patients with hypertension [30]. Diets that replace a portion of NaCl with KCl promote a reduction in blood pressure [31] and prevent cardiovascular events [32].

Potassium-sparing diuretics, such as amiloride and triamterene, which are epithelial sodium channel inhibitors, have been used for decades but have not achieved widespread use in clinical practice. A randomized controlled trial found that a thiazide associated with amiloride was more effective than both placebo and atenolol in preventing cardiovascular events in elderly patients. [33]. In the INSIGHT trial [34] the combination of amiloride and hydrochlorothiazide was more effective than a presentation with slow-release nifedipine in preventing myocardial infarction and heart failure.

An open question is whether amiloride has a blood pressure-lowering effect. In an aggregated data meta-analysis, with only 496 participants, there was no effect of low doses of amiloride and triamterene [35]. In a network meta-analysis of 267 randomized controlled trials, with 58,807 participants, the combination of potassium-sparing agents with thiazide diuretics enhanced their blood pressure-lowering effect. Still, it included aldosterone antagonists among the potassium-sparing agents. [36]. Strictly, our trial cannot discard a blood pressure-lowering effect, because there was no placebo comparator. The absence of any trend for a higher blood pressure-lowering effect with doubling the dose of amiloride suggests that this effect is small and irrelevant from a clinical perspective.

The decrease in serum potassium levels is associated with increased serum glucose. [21]. In the network meta-analysis, Amiloride counteracted the reduction of serum potassium levels and the increase in blood glucose caused by thiazide diuretics. [36]. In the study Pathway-3 [23], amiloride at doses of 10 and 20 mg antagonized the effects of hydrochlorothiazide at doses of 12.5 and 25 mg, respectively. Still, serum potassium decreased moderately in both PREVER trials [15, 22], which were the longest randomized trials involving the combination of chlorthalidone and amiloride in a dosing ratio of 1:5. In this trial, both doses of amiloride antagonized the decrease in blood levels of potassium and the increase in blood glucose during a shorter treatment period.

In conclusion, this study provides robust evidence that chlorthalidone and hydrochlorothiazide, in a dosing ratio of 1:2, have similar effects on blood pressure and laboratory parameters. Amiloride, at doses of 5 and 10 mg, effectively antagonized the hypokalemia and increase in serum glucose induced by chlorthalidone and hydrochlorothiazide. The similar effects of these doses on blood pressure suggest that amiloride has, at best, a weak blood pressure-lowering effect.

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7. OUTROS ARTIGOS PUBLICADOS

The role of angiotensin receptor blockers in CVD risk management

Bottino LG, Fuchs FD. The role of angiotensin receptor blockers in CVD risk management. Expert Rev Cardiovasc Ther. 2020;18(4):181-185. doi:10.1080/14779072.2020.1750369

Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: a protocol for a factorial randomized controlled trial

Martins VM, Helal L, Ferrari F, Bottino LG, Fuchs SC, Fuchs FD. Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: a protocol for a factorial randomized controlled trial. Trials. 2019; 20:736.

Martins *et al. Trials* (2019) 20:736
https://doi.org/10.1186/s13063-019-3909-z

Trials

STUDY PROTOCOL Open Access

Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: a protocol for a factorial randomized controlled trial

Vítor Magnus Martins[1*], Lucas Helal[1], Filipe Ferrari[1], Leonardo Grabinski Bottino[1], Sandra Costa Fuchs[1] and Flávio Danni Fuchs[1,2]

Abstract

Background: Thiazide diuretics have demonstrated favorable blood pressure lowering efficacy, but the equivalent doses of their more common agents, chlorthalidone and hydrochlorothiazide, are still unclear. Further, concerns exist regarding adverse metabolic effects, which may be attenuated with the concomitant administration of a potassium-sparing diuretic, such as amiloride. This trial aims to investigate the efficacy of chlorthalidone and hydrochlorothiazide, in combination with amiloride at different doses, for initial management of patients with primary hypertension.

Methods/design: This is a factorial (2 × 2) randomized double-blinded clinical trial comparing the association of a thiazide diuretic (chlorthalidone 25 mg/day or hydrochlorothiazide 50 mg/day) with a potassium-sparing diuretic (amiloride 10 mg/day or amiloride 20 mg/day) in patients with primary hypertension. The primary outcome will be the mean change from baseline in 24-h systolic and diastolic blood pressure measured by ambulatory blood pressure monitoring. The secondary outcomes will be the mean change from baseline in daytime and nighttime systolic and diastolic blood pressure measured by ambulatory blood pressure monitoring, mean change from baseline in systolic and diastolic blood pressure measured by office blood pressure, incidence of adverse events, variation of laboratory parameters, and proportion of patients who achieved blood pressure control. The follow-up will last 12 weeks. For a P alpha of 0.05, power of 80%, standard deviation of 9 mmHg, and absolute difference of 6 mmHg on systolic blood pressure on 24-h ambulatory blood pressure monitoring, it will be necessary to study a total of 76 patients. The sample size will be increased by 10% to compensate for losses, resulting in 84 patients being randomized.

(Continued on next page)

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Thiazide diuretics alone or combined with potassium-sparing diuretics to treat hypertension: a systematic review and network meta-analysis of randomized controlled trials

Martins VM, Ziegelmann PK, Ferrari F, Bottino LG et al. Thiazide diuretics alone or combined with potassium-sparing diuretics to treat hypertension: a systematic review and network meta-analysis of randomized controlled trials. J Hypertens. 2023;41(7):1108-1116. doi:10.1097/HJH.0000000000003436

Original Article

OPEN

Thiazide diuretics alone or combined with potassium-sparing diuretics to treat hypertension: a systematic review and network meta-analysis of randomized controlled trials

Vítor M. Martins[a], Patrícia K. Ziegelmann[a,b], Filipe Ferrari[a], Leonardo G. Bottino[a,c], Marcelo B. Lucca[a,c], Henrique L. Ruchaud Correa[c], Gabriela B. Blum[c], Lucas Helal[a,d], Sandra C. Fuchs[a,b,c], and Flavio D. Fuchs[a,c,e]

Background: The magnitude of blood pressure (BP)-lowering effects and decrease of the adverse effects of thiazide diuretics provided by potassium-sparing diuretics remain uncertain. The aim of this study was to compare the BP-lowering efficacy and the incidence of adverse effects of high (T+) and low-dose (T-) thiazide diuretics, alone or combined with high (PS+) or low-dose (PS-) potassium-sparing diuretics in patients with primary hypertension.

Methods: A systematic literature search was performed in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, Embase, Web of Science, Scopus and LILACS. Randomized double-blind placebo or active-controlled trials (RCT) with 3 weeks to 1 year of follow-up were included. Sample size, mean and standard deviation from baseline, follow-up and change from baseline values were extracted by two independent reviewers. Pairwise random effect models and Bayesian network meta-analysis models were used to compare the effects of treatments. The risk of bias in individual studies was assessed using the Rob 1.0 tool. The primary outcome was the mean difference in office SBP. Secondary outcomes were the mean difference in biochemical parameters and the incidence of nonmelanoma skin cancer.

Results: Two hundred and seventy-six double-blind RCTs involving 58 807 participants (mean age: 55 years; 45% women) were included. All treatment groups were more effective than placebo in lowering BP, with mean differences (MDs) of change from baseline ranging from −7.66 mmHg [95% credible interval (95% CrI), −8.53 to −6.79] for T- to −12.77 mmHg (95% CrI, −15.22 to −10.31) for T+PS-. T+ alone or combined with potassium-sparing was more effective in reducing BP than T-. The surface under the cumulative ranking curve (SUCRA) estimated ranking showed that the best effectiveness in lowering SBP was found for T+PS- (0.69), T+PS+ (0.65) and T+ (0.54). Compared with placebo, all treatments (except T-PS-) were associated with more potassium reduction and T+ compared with all other treatments and T- when compared with T-PS-. Compared with placebo, all active treatments (except T+PS+) showed higher elevations of uric acid. The increase of plasma glucose promoted by thiazides alone was reduced by potassium-sparing agents.

Conclusion: Thiazides with potassium-sparing diuretics are associated with increased BP-lowering efficacy compared with thiazides alone while minimizing hypokalaemia and hyperglycaemia. These findings demonstrate that thiazide and potassium-sparing diuretic combination is preferable to thiazide alone in treating hypertension.

Keywords: blood pressure, diuretics, hypertension, potassium-sparing, thiazides, treatment

Abbreviations: BP, blood pressure; CrI, credible interval; PRISMA-NMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses for Network Meta-analysis; PROSPERO, International Prospective Register of Systematic Reviews; PS-, low-dose potassium-sparing diuretics; PS+, high-dose potassium-sparing diuretics; RCTs, randomized controlled trials; RoB, Risk of Bias; SUCRA, The surface under the cumulative ranking curve; T-, low-dose thiazide diuretics; T+, high-dose thiazide diuretics

INTRODUCTION

Thiazide diuretics and thiazide-like diuretics (e.g. chlorthalidone and indapamide) were the primary drugs tested in landmark randomized controlled

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Optimizing Nephron Performance: The Old, the New, and the 2 New-old Diuretic Therapies

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Article

Optimizing Nephron Performance: The Old, the New, and the New-old Diuretic Therapies

Short Title: Optimizing Nephron Performance

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Abstract: Pharmacological influence on nephron function has modified the clinical course of hypertension, heart failure, and chronic kidney disease. (CKD). This is a review of the efficacy of old diuretics and the incremental efficacy of new diuretics in managing hypertension, heart failure, and CKD, concluding with new evidence on the effectiveness of old agents. The efficacy of "older" diuretic agents, such as thiazide and loop diuretics, on heart failure and CKD has been primarily explored in nonrandomized studies. However, the efficacy of these agents and indapamide, a slightly newer but still "old" diuretic in preventing blood pressure-related cardiovascular disease, has been demonstrated in randomized controlled trials. Potassium-sparing agents counteract some of the adverse effects of thiazides and have been shown to prevent cardiovascular events in patients with heart failure. Newer drugs with a diuretic effect, such as gliflozins, act through a new mechanism of action in the kidney and have shown efficacy in controlling symptoms and preventing cardiovascular events in patients with heart failure, regardless of diabetes. Furthermore, gliflozins have prevented the progression of chronic kidney disease in patients with and without diabetes mellitus. New evidence detailing the efficacy of old agents has emerged. Chlorthalidone had a large blood pressure-lowering effect in patients with stage IV CKD. Acetazolamide was effective in accelerating the clinical control of patients with acute heart failure, including patients with some reduction in kidney function. We anticipate investigating the comparative impact of combining different agents to optimize nephron function in the future.

Keywords: Nephrons; diuretics; blood pressure; hypertension; heart failure; chronic kidney disease

1. Introduction

Diuretics have been in use for more than seven decades and include thiazide and thiazide-like diuretics, loop diuretics, potassium-sparing diuretics, and acetazolamide. Gliflozins (sodium-glucose co-transporter 2 – [SGLT2] inhibitors)1 and newer

8. CONCLUSÕES

Este estudo demonstrou que a clortalidona (25 mg) e a hidroclorotiazida (50 mg), na proporção de dose 1:2, apresentam eficácia e segurança semelhantes na redução da pressão arterial, avaliada por monitorização ambulatorial e em consultório, bem como nos parâmetros bioquímicos e na incidência de efeitos adversos em pacientes com hipertensão arterial. Da mesma forma, as doses de amilorida (5 mg e 10 mg) mostraram efeitos comparáveis na pressão arterial e nos parâmetros metabólicos, com eficácia significativa em antagonizar a hipocalemia e a hiperglicemia induzidas pelos diuréticos tiazídicos, embora com efeito hipotensor fraco ou ausente. Esses achados reforçam a intercambiabilidade entre clortalidona e hidroclorotiazida

em doses equipotentes e destacam o papel da amilorida como um adjuvante seguro e eficaz na mitigação de efeitos adversos metabólicos, contribuindo para a otimização do tratamento anti-hipertensivo.

9. CONSIDERAÇÕES FINAIS

Os resultados desta tese preenchem lacunas importantes na literatura sobre o manejo da hipertensão arterial, confirmando a equivalência entre clortalidona e hidroclorotiazida em doses proporcionais e elucidando o papel da amilorida na prevenção de complicações metabólicas associadas aos tiazídicos. Esses dados têm implicações diretas na prática clínica, apoiando a escolha informada de diuréticos tiazídicos e a associação com amilorida para um tratamento mais seguro e eficaz. Futuros estudos poderiam explorar doses ainda mais baixas de amilorida ou sua combinação com outras classes anti-hipertensivas, bem como avaliar desfechos cardiovasculares de longo prazo em populações mais diversas.