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EFEITO DE ANTI-HIPERTENSIVOS NA APNEIA DO SONO: ENSAIO CLÍNICO RANDOMIZADO

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“Ideias, e somente ideias, podem iluminar a escuridão.”

Ludwig von Mises, em As Seis Lições

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

AHI: apnea-hypopnea index

ANP: peptídeo natriurético atrial

BP: blood pressure

CI: Confidence Interval

CPAP: aparelho de pressão positiva contínua na via aérea

DOSA: Diuretics Over Sleep Apnea

ECA: enzima conversora de angiotensina

ECR: ensaio clínico randomizado

ECRs: ensaios clínicos randomizados

HAS: Hipertensão Arterial Sistêmica

HCPA: Hospital de Clínicas de Porto Alegre

HDL: high-density lipoprotein

hsCRP: high-sensitive C Reactive Protein

IAH: Índice de Apneia-Hipopneia

IC: Intervalo de Confiança

MAPA: monitorização arterial de pressão arterial

NT-proBNP: N-terminal pro b-type natriuretic peptide

OSA: Obstrutive sleep apnea

PAD: pressão arterial diastólica

PAS: pressão arterial sistólica

PSG: Polissonografia

SAHOS: Síndrome de Apneia-Hipopneia Obstrutiva do Sono

RESUMO

INTRODUÇÃO: Apneia-hipopneia obstrutiva do sono (SAHOS) e hipertensão são prevalentes, associadas aaumento do risco cardiovascular e relacionadas com hiperativação simpática e retenção hídrica. Há evidência de baixa qualidade que redução da retenção hídrica pode melhorar SAHOS. Nós exploramos a hipótese que diuréticos, que reduzem a água corporal, são mais eficazes que anlodipino, um anti-hipertensivo implicado com edema, para controlar SAHOS em pacientes hipertensos.**MÉTODOS**: Ensaio clínico comparando Clortalidona/Amilorida 25/5mg (C)*versus* Anlodipino 10mg (A)na SAHOS medida por monitor portátil e pressão arterial medida por monitorização ambulatorial 24h. Foram selecionados pacientes acima de 40 anos, com hipertensão estágio I (140-159/90-99mmHg) e SAHOS moderada (10-40 apneias/hora). Os desfechos primários forama variação do número de apneias/hora (IAH) e da pressão arterial (PA) em 8 semanas.**RESULTADOS**: Os pacientes randomizados para diurético ou anlodipino foram semelhantes na idade, sexo e demais características. Não houve diferença na variação do IAH após 8 semanas (C26,1 *versus*A24,1; P=0,578). Não houve diferença PA sistólica (C 122,2 *versus* A 125,3; P=0,184) ou diastólica (C 122,2 *versus* A 125,3; P=0,184) de 24h.Houve redução do IAH no subgrupo de SAHOS grave de 12,3 eventos/h (95% IC: 2,0-22,7; P=0,028), sem diferença entre os fármacos.**CONCLUSÕES**: Clortalidona/Amiloridaou Anlodipino não têm efeito no IAH em pacientes com SAHOS moderada e possuem semelhante eficácia de curto prazo na redução da pressão arterial. A eficácia em SAHOS mais grave necessita ser demonstrado em futuros ensaios clínicos randomizados.

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1. INTRODUÇÃO

Síndrome de apneia-hipopneia obstrutiva do sono (SAHOS) é tão frequente quanto a Hipertensão Arterial Sistêmica (HAS), mas é ainda mais subdiagnosticada e subtratada. Essa tese explora efeito terapêutico comum a SAHOS e HAS, dado o compartilhamento de mecanismos fisiopatológicos entre as duas condições clínicas.

Tendências genéticas à retenção hidrossalina renal, muitas vezes associada à ativação simpática, somado à dieta rica em sódio, estão intimamente relacionados a patogênese da HAS. Esses fatores estão também presentes na fisiopatologia da SAHOS, através do deslocamento noturno rostral dos fluídos que se depositam nos membros inferiores durante o dia. Apesar de inúmeras demonstrações fisiopatológicas, não há estudos bem desenhados propondo intervenções farmacológicas para SAHOS abordando esses mecanismos.

Para tanto, desenhamos ensaio clínico randomizado para testar se combinação de clortalidona com amilorida sobrepuja anlodipino na redução de apneias ou hipopneias durante o sono em pacientes com SAHOS moderada e HAS estágio I. Desfechos foram avaliados por monitor portátil de polissonografia validado e monitorização ambulatorial de pressão arterial (MAPA). Avaliou-se adicionalmente sonolência diurna, problema decorrente de SAHOS, e bateria de parâmetros laboratoriais, para comparar a segurança dos tratamentos.

Essa tese pretende contribuir com o conhecimento fisiopatológico compartilhado entre SAHOS e HAS e gerar conhecimento que possa ser utilizado no atendimento de pacientes.

2. REVISÃO DA LITERATURA

Estudo populacional realizado na cidade de São Paulo estimou que 1 em cada 3 adultos apresenta mais que 5 apneias ou hipopneias durante o sono,sendo portador da Síndrome de Apneia-Hipopneia Obstrutiva do Sono (SAHOS). SAHOS moderada ou grave foi encontrada em 16,9% dos indivíduos(1). Hipertensão Arterial Sistêmica (HAS) tem prevalência semelhante, próxima a 30% da população adulta brasileira, considerando o tradicional ponto de corte de 140/90mmHg(2).

SAHOS é caracterizada por cessação ou marcada redução do fluxo aéreo durante a noite, provocando hipoxemia e despertares,associando-se à sonolência diurna, piora da qualidade de vida, aumento do risco cardiovascular (3), arritmias cardíacas e insuficiência cardíaca (4). Estima-se que o risco de infarto ou acidente vascular cerebral aumente em torno de 90%, e a mortalidade, em torno de 60%, em portadores de SAHOS (5). Além desses riscos, SAHOS também é considerada causa de HAS secundária pelas diretrizes (6-8).Quantifica-se SAHOS pelo Índice de Apneia-Hipopneia (IAH), considerando-se leve o IAH entre 5 e 14, moderada entre 15 e 30 e severa mais que 30 eventos por hora de sono (9). Para ser considerada apneia, sua duração deve ser de ao menos 10 segundos, e representar redução maior que 50% no fluxo aéreo. Caso não atingir 50% de redução no fluxo aéreo, mas for associada ou a uma dessaturação >3%, ou a um despertar, é considerada uma hipopneia (10).

SAHOS é encontrada entre 30-80% dos hipertensos (11). Dentre pacientes ambulatoriais, a prevalência é de 7% nos não hipertensos e de 30% nos hipertensos (12). No ambulatório de HAS do Hospital de Clínicas de Porto Alegre (HCPA), SAHOS foi diagnosticada em 38% dos hipertensos controlados e 71% dos hipertensos resistentes (13). Em avaliação sistemática de hipertensos resistentes, SAHOS foi a principal causa, sendo encontrada em 64% dos pacientes (14). Dentre os portadores de SAHOS, 36% são

hipertensos, comparativamente a 13% no grupo dos roncadores sem SAHOS e 7% no grupo dos não-roncadores sem SAHOS (15). Cada apneia ou hipopneia por hora de sono aumenta em torno de 4% o risco da ocorrência de HAS (16). A associação entre SAHOS e HAS, com claro efeito dose resposta, foi confirmado em estudos de coorte de grande porte (17, 18).

A polissonografia (PSG) é o padrão ouro no diagnóstico de SAHOS (3, 19). Sem ela muitos profissionais deixarão de diagnosticar essa patologia (20). Trata-se de exame custoso, que requer colaboração do paciente e necessita de laboratório específico pouco disponível (12, 20). O emprego de monitores portáteis que avaliam variáveis ventilatórias (esforço ventilatório, fluxo na via aérea, ocorrência de ronco), saturação de hemoglobina (oximetria de pulso), frequência cardíaca e a posição do paciente são cada vez mais utilizados e apresentam sensibilidade de 88 a 100% e especificidade de 79 a 88% (21-24). Foi validado por nosso grupo em 2009 o dispositivo Somnocheck (Weinmann medical technology, Hamburgo, Alemanha), que apresentou sensibilidade de 96% e especificidade de 64%, comparativamente a polissonografia em laboratório, para o exame realizado no domicílio(24).

O uso noturno de aparelho de pressão positiva contínua na via aérea (CPAP) é o tratamento padrão da SAHOS (25). Sua adesão em curto-prazo situa-se entre 50 a 80% dos pacientes, sendo menor naqueles com IAH baixo, sem história de ronco e sonolência diurna (26), abrindo possibilidades para uso de outros tratamentos (27). Revisão Cochrane identificou somente pequenos estudos, de baixa qualidade,sem efeito consistente de nenhum fármaco no tratamento da SAHOS(27). Fluticasona, naltrexona, fisiostigmina e lubrificante nasal reduziram discretamente o IAH, com discutível relevância clínica(27). Atualização desta revisão(28)identificou algumas medicações com discretos efeitos como donazepil, ondansetrona/fluoxetina e paroxetina, sem, no entanto, recomendar nenhuma

especificamente. A redução de IAH encontrada nos fármacos efetivos foi entre 6-14 eventos por hora de sono. No tratamento medicamentoso da SAHOS, diferentemente do CPAP, deve-se considerar os mecanismos no indivíduo para escolha de terapêutica alternativa (27, 28), o que fundamenta a realização da presente tese.

A associação entre SAHOS e HAS foi explorada em múltiplos ensaios clínicos randomizados com CPAP, tendo pressão arterialaferida porMAPA como desfecho. Considerando os 44 ensaios clínicos randomizados (ECRs) comparados com controles inativos, CPAP reduz a pressão arterial sistólica (PAS) em 2,5mmHg e a pressão arterial diastólica (PAD) em 2,0mmHg. A mesma meta-análise avaliou também dispositivos de avanço mandibular, testado em 7 ECRs, com resultados semelhantes (29). Análogo resultado foi encontrado em recente meta-análise limitando os ECRs aos que incluíssem apenas indivíduos hipertensos, com redução de PAS em 2,3mmHg e de PAD em 2,0mmHg (30). Ao restringir os ECRs aos que estudassem apenas hipertensos resistentes, o efeito foi de 4,7mmHg na PAS e 3,0mmHg na PAD (31). Apesar de a pressão basal se associar com o efeito anti-hipertensivo do CPAP, o principal fator associado à redução de pressão arterial é o tempo de uso do aparelho, aumentando o efeito em 1,5mmHg na PAS e 0,9mmHg na PAD por hora adicional à média(29).

Alterações no sistema nervoso autônomo encontradas na SAHOS poderiam explicar a associação com HAS e eventos cardiovasculares (32).Há crescente sobre técnica de ablação simpática renal por radiofrequência, associada à redução da PA em 33/11 mmHg em hipertensos resistentes (33), e do IAH de 16,3 para 4,5 em análise de subgrupo de 10 pacientes com SAHOS associada(34). Comparação retrospectiva chinesa comparou ablação simpática (15 indivíduos) com CPAP (16 indivíduos), com efeito mais modesto para ablação (IAH de 32 para 27) que CPAP (IAH de 35 para 5). Entretanto, o efeito anti-hipertensivo da ablação foi mais intenso (12 *versus* 6mmHg) (35). Especula-se que o

bloqueio aferente simpático renal, que reduz a avidez por sal e, consequentemente, o volume total de fluidos corporais, seja o responsável pela melhora da SAHOS.

Análise conjunta destes e outros 3 estudos observacionais, totalizando 49 pacientes, identificou redução média no IAH de 9,6(36). O ECR Symplicity HTN-3 testou adequadamente ablação simpática renal comparativamente a procedimento placebo, havendo modesta e não significativa redução de 2,0mmHg na PAS de 24h (37).Nos pacientes com SAHOS, que constituíram aproximadamente 30% da amostra, o efeito anti-hipertensivo adicional ao placebo na PAS de 24h foi de 4,2mmHg nos pacientes com SAHOS comparado com 0,7mmHg nos demais pacientes (38). Assim, apesar dos efeitos anti-hipertensivos serem discretos para um procedimento invasivo, a relevância do bloqueio simpático na SAHOS ainda não foi esclarecida adequadamente(39). Modelo animal com suínos demonstrou que ablação simpática, e não atenolol, suprimiu a elevação de pressão arterial pós apneia(40), mecanismo que pode explicar as maiores diferenças na redução de pressão arterial durante a noite no subgrupo SAHOS do estudo Symplicity HTN-3 (38). Há evidências também do envolvimento do sistema renina-angiotensina-aldosterona, provavelmente também associada ao estímulo simpático, pois o bloqueio dos receptores AT1 de angiotensina evitou a elevação de pressão arterial média em 9 voluntários saudáveis submetidos a hipóxia (7,9mmHg com placebo e -0,2mmHg com losartana)(41). Esse efeito possivelmente seja mais intenso em pacientes portadores de SAHOS, pois o efeito pressor das hipoxemias correlaciona-se positivamente com o número de apneias (42). Estudos observacionais e pequenos ensaios clínicos geram, no máximo, hipótese sobre a eficácia de denervação renal, e requerem estudos pelo menos de qualidade equivalente ao Symplicity HTN-3 para demonstrar eficácia.

São múltiplos os mecanismos fisiopatológicos comuns entre HAS e SAHOS(43). Além da hiperativação simpática, descreveu-se disfunção endotelial, estresse oxidativo

vascular, inflamação sistêmica, coagulopatias e distúrbios metabólicos (4, 44).Dentre esses inúmeros marcadores clínicos e bioquímicos, encontra-se também a elevação do peptídeo natriurético atrial (ANP) (43). O ANP é liberado pelos miócitos atriais, quando distendidos por pressão atrial elevada. O aumento do retorno venoso devido às pressões negativas intratorácicas durante as apneias pode ser a razão do aumento dos níveis de ANP em pacientes com SAHOS. Níveis elevados de ANP na SAHOS são revertidos pelo uso de CPAP (45). Em resumo, esses mecanismos provocados por SAHOS, que explicam as lesões vasculares, são essencialmente explicadas por 3 mecanismos: hipóxia intermitente, pressões intratorácicas negativas intensas e despertares noturnos (4, 46). A semelhança na fisiopatologia e nas lesões em órgão alvo da SAHOS comoutros distúrbios vasculares, deveriam ser suficientes para considerá-la doença cardiovascular (47).

Independente dos mecanismos subjacentes que possam provocar retenção hídrica, o papel dos fluidos extravasculares na gênese das apneias obstrutivas tem sido investigado. Durante a noite, o volume de líquido acumulado nos membros inferiores se reduz enquanto o perímetro cervical aumenta. Esse deslocamento de fluidos no sentido rostral durante o decúbito noturno aumenta a pressão perifaríngea e a colapsabilidade da via aérea superior (48-51). A redução de volume de fluido nas pernas através de compressores pneumáticos de membros inferiores em 13 homens saudáveis aumentou o perímetro do pescoço e a colapsabilidade da via aérea (49). O uso desse tipo de dispositivo para provocar o deslocamento de fluídos foi repetido em diferentes populações com resultados semelhantes (48, 52, 53). Apesar do maior interesse nos últimos anos, a descrição do deslocamento de fluídos com decúbito data dadécada de 50, quando descreveu-se um aumento médio de 0,5mm na espessura do lobo da orelha durante a noite (54).

Coorte de 15 hipertensos controlados e 25 hipertensos resistentes demonstrou aumento do perímetro cervical respectivo de 1,1 e 1,5cm e redução do volume da perna de 175,8 e 346,7mL após o sono. O IAH correlacionou-se com o deslocamento de volume dos membros inferiores para a região cervical em ambos os grupos (R^2=0,56, P<0,0001) (55). O uso de CPAP não previne o deslocamento de volume de membros inferiores. Entretanto, previne o aumento do perímetro cervical, com magnitude associada à redução do IAH (51).Outra proposta terapêutica seria o uso de meias elásticas, que reduziram IAH em duas pequenas séries de caso (56, 57). O aumento do perímetro cervical no decúbito se correlaciona ao IAH com coeficiente de 0,37 (58). Hipertensos resistentes tendem a ter SAHOS mais frequentemente, e com maior gravidade, que hipertensos leves, devido ao fato de apresentarem menores áreas seccionais faríngeas relacionadas ao maior deslocamento de fluídos, aumentando a probabilidade de obstrução das vias aéreas superiores durante o sono (59).

Idade e sexo interferem na colapsabilidade das vias aéreas. Com o envelhecimento, há aumento na gordura perifaríngea e redução da atividade do nervo genioglosso (60). Essas alterações anatômicas relacionadas à idade aumentam a colapsabilidade das vias aéreas, com uma correlação de 0,69 entre a idade e a pressão de oclusão faríngea. ECR cruzado comparando a resposta a infusão de 22mL/kg solução salina durante a noite com infusão mínima em jovens e idosos só encontrou aumento significativo do IAH em indivíduos com mais de 40 anos (32 *versus* 2) (61). Mulheres jovens têm menor probabilidade de apresentar colapso da via aérea com o deslocamento rostral de fluídos provocado por compressor de membros inferiores(52). Em indivíduos com insuficiência cardíaca, correlacionou-se deslocamento de fluídos com perímetro cervical e IAH apenas em homens (62). Sabe-se também que mulheres tem menos deslocamento rostral de fluídos que homens(63). Apesar das menores áreas seccionais faríngeas encontradas na

mulher não se correlacionarem com piora da SAHOS como no homem (64), a pressão de colapsabilidade é semelhante quando comparados os sexos (65).

No passado creditou-se à testosterona o aumento do risco de SAHOS (66). Entretanto, o bloqueio androgênico não foi eficaz em reduzir esse risco(67).Entre outros fatores que podem confundir a associação das mudanças nos fluídos com a piora da SAHOS é a obesidade. Obesos com ou sem SAHOS não apresentam diferença no deslocamento rostral de fluídos, não apresentando a observada correlação com o IAH em outros estudos (68). Obesos com SAHOS têm maior volume de língua, com maior deposição de gordura que obesos sem SAHOS (69). Adicionalmente existe a interferência da variação de peso, bem avaliada em 2 coortes (70, 71). Na primeira foram acompanhados 690 pacientes por 4 anos, encontrando uma variação de aproximadamente 30% no IAH acompanhando a variação de 10% do peso corporal total, ajustando para outras variáveis (70). Outra coorte com quase 3000 participantes, encontrou variação menos intensa em mulheres que homens (71). Portanto, não são claro os motivos das diferenças na SAHOS entre homens e mulheres (67).

Condições que propiciam hipervolemia como insuficiência cardíaca (51), e insuficiência renal (72) aumentam tanto a probabilidade de apneia central quanto obstrutiva. O mecanismo da SAHOS é o explicitado acima, relacionado ao acúmulo cervical de fluídos. As apneias centrais são ocasionadas por menores valores de pCO2 relacionados à hiperventilação necessária para evitar hipoxemia secundária a congestão pulmonar, dificultando os gatilhos respiratórios via hipercapnia (51). A retirada de fluídos via ultrafiltração é eficaz em reduzir as apneias. A retirada,via ultrafiltração, de 2L de fluídos, em 15 pacientes com insuficiência renal, sem hemodiálise associada, reduziu o IAH de 44 para 17 (73).A sobrecarga de sódio também se associa com gravidade da SAHOS nesses pacientes (74, 75), presumidamente ligada a piora da retenção hídrica. A

quantidade de água perifaríngea medida por ressonância nuclear magnética se correlaciona com IAH com um coeficiente de 0,54 (76).

Além de extensa literatura que descreve vínculo fisiopatogênicoentre SAHOS em indivíduos hipertensos com retenção de fluídos nos membros inferiores e deslocamento rostral em decúbito, há algumas intervenções farmacológicas potencialmente efetivas (77).Como prova de conceito, administrou-se o diurético espironolactona 50mg em 12 hipertensos resistentes portadores de SAHOS, observando-se redução do IAH de 40 para 22 após 8 semanas (78). Outro estudo não controlado administrou dois diuréticos (metolazona 5mg e espironolactona 50mg) para 16 hipertensos com IAH >20, reduzindo o IAH de 58 para 48 após 2 semanas, com benefício proporcional à redução no volume de fluído nos membros inferiores (79). O efeito de curto prazo com diuréticos também foi testado com furosemida intravenosa 20mg e espironolactona 100mg duas vezes ao dia em 15 hipertensos, portadores de SAHOS grave e insuficiência cardíaca diastólica. Após três dias o IAH caiu de 74 para 57, paralelo com redução do peso corporal e aumento da área faríngea (80).Em série de nove casos, a troca de inibidor da enzima conversora de angiotensina (ECA) por hidroclorotiazida 25mg associada à espironolactona 25mg levou a redução de 34 para 20 no IAH dos indivíduos com tosse, enquanto o manteve por volta de 34 no indivíduos sem tosse (81).O uso de Inibidores da ECA está associado à inflamação nas vias aéreas, especialmente em indivíduos que apresentam tosse (81). Esse efeito deletério parece ser restrito aos que apresentarem tosse, já que série de 6 pacientes reduziu o IAH de 31 para 20 após o uso de cilazapril (82). Em 1990 o mesmo grupo fez o primeiro ECR comparando anti-hipertensivos, testando cilazapril ou metoprolol em 6 pacientes, e reduzindo respectivamente o IAH de 54 para 40 e de 45 para 34 após 8 dias de tratamento (83). No ano seguinte foi publicado estudo semelhante pelos mesmos

autores, que pareceu continuação do mesmo ECR, com 12 pacientes, e redução de 40 para 27 e 26 com Cilazapril e Metoprolol respectivamente (84).

O primeiro ECR com diurético foi realizado em 1988, quando foram randomizados 10 participantes com SAHOS de forma cruzada, para 2 semanas de placebo, acetazolamida 250mg 4 vezes/dia e protriptilina 20mg. Não houve diferença no IAH entre placebo e protriptilina (50 *versus* 46), mas houve significativa redução de 24 apneias no grupo acetazolamida (85). Diferentes anti-hipertensivos e seus efeitos no IAH foram comparados em interessante ECR realizado no ano 2000. Foram randomizados 40 hipertensos com IAH médio de 42 para sequências de 2 fármacos, para serem usados por 6 semanas, com *washout* de 3 semanas entre os tratamentos. Foram testados atenolol 50mg, anlodipino 5mg, enalapril 20mg, hidroclorotiazida 25mg e losartana 50mg. A única diferença significativa foi entre anlodipino que reduziu o IAH em 5,9 e Losartana que aumentou em 5,3. As demais diferenças foram pequenas e não significativas (reduções entre 1,5 e 2,2) (86). Outro ECR com 31 pacientes com HAS e SAHOS demonstrou outras tendências, sem diferença estatisticamente significativa, com nebivolol aumentando o IAH de 23 para 28, enquanto valsartana reduziu de 24 para 22 (87). A hipótese de que inibidor da ECA poderia interferir diferencialmente na SAHOS também não foi confirmada em pequeno ECR cruzado de 16 pacientes utilizando doxasosina ouenalapril, que não reduziram significativamente o IAH como desfecho secundário (88). Outro ECR cruzado de 18 indivíduos testando atenolol, isradipino, hidroclorotiazida, spirapril concluiu que houve muita heterogeneidade e pequenas diferenças entre os fármacos para realizar análises (89).

Espironolactona parece ter efeito superior a outros anti-hipertensivos. ECR aberto chinês, com controles sem tratamento adicional, em hipertensos resistentes demonstrou que Espironolactona 20mg aumentada para 40mg se necessário reduziu o IAH de 37 para

15, comparado com 40 para 38 nos controles(90).Existem ainda outros 2 ECR concluídos(91, 92), ainda não publicados, que testam o efeito de anti-hipertensivos e fluídos na SAHOS. O primeiro comparou anlodipino 10mg e clortalidona/amilorida 25/5mg em hipertensos com SAHOS objetivando reduzir o IAH após 8 semanas e é o tema da presente tese(91). O segundo estudou portadores de SAHOS grave, sem necessariamente HAS, comparando o efeito de placebo com orientação de dieta hipossódica ou Espironolactona 100mg com Furosemida 20mg no IAH após 1 semana (92).Ambas intervenções reduziram a água corporal total e o IAH. Dieta reduziu IAH de 48 para 37, diuréticos, de 50 para 43, enquanto placebo manteve em 49 (93).

Três meta-análises demostraram a eficácia de medidas não farmacológicas na melhora da SAHOS (94-96). Orientação de atividade física foi avaliada em 5 estudos intervencionais (3 ECR), incluindo 129 pacientes, demonstrando redução média de 6 no IAH (96). Mudança de estilo de vida foram avaliadas em 4 ECR que reduziram 14kg no peso e 16 no IAH (94). Cirurgia bariátrica foi ainda mais efetiva. Na avaliação de 342 pacientes em 12 estudos, o índice de massa corporal médio baixou de 55 para 38kg/m² com consequente melhora no IAH de 55 para 16 (95).

Outros 2 ECR avaliaram a eficácia de medidas não farmacológicas no IAH e seus efeitos nos fluídos(97, 98). O primeiro testou os efeitos do exercício físico aeróbico diário após 4 semanas. Na análise por protocolo (foram randomizados 44 participantes, mas apenas 17 por grupo concluíram a pesquisa), o grupo intervenção reduziu o IAH de 25 para 17, enquanto o controle manteve o IAH de 21. Houve também redução do volume de fluídos nas pernas de 4,83 para 4,58L, deslocamento rostral de 580 para 460mL e aumento na área das vias aéreas superiores pela manhã de 2,4 para 2,9cm² (97). Outra alternativa não farmacológica é o uso de meias elásticas. ECR testou o efeito de meias compressivas por 2 semanas, incluindo 57 indivíduos, promovendo redução do IAH de 32

para 24, comparativamente a ausência de mudança no grupo controle. De forma interessante, seus efeitos foram mais tênues que os do exercício no volume de fluídos nas pernas, reduzindo de 5,3 para 5,2L, mas foram semelhantes na redução no deslocamento rostral durante a noite (570 para 490mL)(98).

Na seleção de anti-hipertensivos no tratamento inicial de HAS,clortalidona foi o mais eficaz na prevenção de diversos eventos cardiovasculares no melhor ECRrealizado dirigido a avaliação de alternativas de primeira linha no tratamento de HAS(99). No conjunto, diuréticos suplantaram outras opções anti-hipertensivas na prevenção de desfechos cardiovasculares em meta-análise de diversos estudos (100). Há forte evidência de que a intensidade do efeito hipotensor associa-se com a eficácia na prevenção de eventos primordiais (101), como também demonstrado no estudo ALLHAT (99).

O principal efeito adverso de clortalidona é a hipocalemia, que quando ocorreu anulou a eficácia do tratamento no estudo SHEP (102) e provocou a elevação dos níveis séricos de glicose (103). A associação de diuréticos poupadores de potássio pode contornar estes problemas(104). Amilorida, antagonista fisiológico da aldosterona, aumenta a eficácia anti-hipertensiva de diuréticos e é muito bem tolerada, como se mostrou em ensaio clínico realizado em Porto Alegre (105). Clortalidona/amilorida foi mais eficaz que losartana para reduzir a PA em ensaio clínico realizado no Brasil(106).

Anlodipino mostrou-se mais eficaz que valsartano, na prevenção de infarto do miocárdio (IAM) e acidente vascular cerebral (AVC), no estudo VALUE (107). No estudo ALLHAT, anlodipino foi equivalente a clortalidona na prevenção de IAM e AVC (99). No ECR ACCOMPLISH, a combinação de benazepril/anlodipino 5mg mostrou-se superior a benazepril/hidroclorotiazida 12,5mg na prevenção de desfecho composto por IAM, AVC, angina e revascularização coronariana (108).

Clortalidona é mais eficaz em termos de redução da pressão arterial que hidroclorotiazida. Em ensaio clínico com MAPA, 25 mg de clortalidona reduziram a PA sistólica de 24h em mais de 5 mmHg do que 50 mg de Hidroclorotiazida. A diferença foi ainda mais acentuada no período do sono (7,1 mmHg) (109). A consistência destes achados com a de outros estudos demonstra que sequer 25mg de clortalidona e 50 mg de hidroclorotiazida sejam equipotentes.

O conjunto das evidências demonstra que clortalidona e anlodipino são anti-hipertensivos mais efetivos que representantes de outras classes e mesmo dentro de suas classes. Conforme discutido, o uso de anti-hipertensivos no tratamento da SAHOS ainda não foi apropriadamente testado.

Devido à alta prevalência de HAS, SAHOS e sua associação, o agravo à saúde que ambas provocam, barreiras de custo e adesão ao CPAP, propomos um ensaio clínico randomizado utilizando drogas seguras e com ampla demonstração de eficácia e efetividade no tratamento de HAS.Os estudos revisados são confluentes na demonstração das relações entre deslocamento de fluidos e SAHOS. Muitos, no entanto, são simples séries de casos, outros são ensaios clínicos pequenos, e ainda há estudos sem adequado comparador. Assim, configura-se como necessário comparar opções terapêuticas em estudos adequadamente desenhados para identificar superioridade de alguma no controle de SAHOS, paralelamente a avaliação de efeito hipotensor.

A ideia de comparar a associação diurética com anlodipino, dois anti-hipertensivos eficazes, explora a hipótese de que o primeiro, por promover a excreção hídrica, reduziria o edema laríngeo mais eficazmente que anlodipino, anti-hipertensivo que promove edema de membros inferiores em muitos pacientes. Os resultados desse estudo contribuirão para

o estudo da patogênese da apneia do sono, eventualmente orientando a preferência por medicamentos em pacientes hipertensos com SAHOS.

3. QUADRO CONCEITUAL

SAHOS associa-se à retenção de fluídos, que provavelmente se acumulam na perifaringe facilitando seu colapso. A hipóxia intermitente, característica da apneia do sono, gera hiperatividade simpática e aumento de pressão arterial. CPAP diminui episódios de SAOHS e, portanto, a atividade simpática e a pressão arterial, promovendo a excreção de sal e água. Diuréticos podem representar nova forma de abortar este ciclo vicioso, promovendo diretamente a excreção de sal e água. Este quadro conceitual embasa nossa questão de pesquisa.

4. QUESTÃO DE PESQUISA

Diuréticos são efetivos no tratamento da SAHOS comparativamente a bloqueadores do canal de cálcio?

5. OBJETIVOS

Primários

1. Comparar a eficácia da associação de clortalidona e amilorida com anlodipino na redução do IAH.

2. Avaliar a correlação entre redução de PA e IAH independentemente do tratamento empregado.

Secundários

1. Comparar a incidência de efeitos adversos induzidos por anlodipino e clortalidona associada a amilorida em pacientes com hipertensão arterial.

2. Comparar a eficácia de clortalidona associada à amilorida com anlodipino na proteína C reativa ultrassensível e no precursor do peptídeo natriurético cerebral.

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7. ARTIGO 1

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TRIALS

STUDY PROTOCOL Open Access

The effect of antihypertensive agents on sleep apnea: protocol for a randomized controlled trial

Fábio Tremea Cichelero[1], Denis Martinez[1], Sandra Costa Fuchs[1], Miguel Gus[2], Leila Beltrami Moreira[1] and Flávio Danni Fuchs[1,2*]

Abstract

Background: Obstructive sleep apnea (OSA) and hypertension are well-known cardiovascular risk factors. Their control could reduce the burden of heart disease across populations. Several drugs are used to control hypertension, but the only consistently effective treatment of OSA is continuous positive airway pressure. The identification of a drug capable of improving OSA and hypertension simultaneously would provide a novel approach in the treatment of both diseases.

Methods/Design: This is a randomized double-blind clinical trial, comparing the use of chlorthalidone with amiloride versus amlodipine as a first drug option in patients older than 40 years of age with stage I hypertension (140 to 159/90 to 99 mmHg) and moderate OSA (15 to 30 apneas/hour of sleep). The primary outcomes are the variation of the number of apneas per hour and blood pressure measured by ambulatory blood pressure monitoring. The secondary outcomes are adverse events, somnolence scale (Epworth), ventilatory parameters and C reactive protein levels. The follow-up will last 8 weeks. There will be 29 participants per group. The project has been approved by the ethics committee of our institution.

Discussion: The role of fluid retention in OSA has been known for several decades. The use of diuretics are well established in treating hypertension but have never been appropriately tested for sleep apnea. As well as testing the efficacy of these drugs, this study will help to understand the mechanisms that link hypertension and sleep apnea and their treatment.

Trial registration: ClinicalTrials.gov: NCT01896661

Keywords: Sleep apnea, Hypertension, Treatment, Diuretics, Chlorthalidone, Amlodipine

Background

Obstructive sleep apnea (OSA) is a well-known cardiovascular risk factor and a major cause of secondary hypertension [1,2]. About 30% of the population suffers from OSA and it is moderate to severe (more than 15 apneas/hour of sleep) in 16.9% of adults [3]. OSA is observed in 30% to 80% of hypertensive patients [4]. We demonstrated that 38% of patients with controlled hypertension have OSA, in contrast to 71% of patients with resistant hypertension [5]. Each episode of apnea/hour increases the risk of hypertension by 4% [6].

The association between OSA and hypertension has been disregarded by clinicians and even by researchers of hypertension [7]. The high cost and low availability of the golden standard method for diagnosing OSA, full polysomnography, may be one of the reasons [8,9]. The use of portable devices, which have been validated in our laboratory, could circumvent this limitation, since they have reasonable sensitivity (96%) and specificity (64%) [10].

The standard treatment for OSA is continuous positive airway pressure (CPAP) and 46 clinical trials show the benefits [11]. It has also been shown in randomized clinical trials that CPAP lowers blood pressure, particularly in patients with hypertension [12]. Blood pressure decreased by 7.8/5.3 mmHg in the 24 h ambulatory blood pressure monitoring in patients with OSA and hypertension, but did not decrease in those without OSA [13]. The efficacy of CPAP in patients with milder forms of OSA is still unproven [14], which could be secondary to

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the low adherence in the use of the method. Other therapies could be beneficial in such patients [15].

A Cochrane review, which identified 26 clinical trials of 21 drugs totaling 394 patients, failed to identify any pharmacological treatment with consistent efficacy. Some drugs, like fluticasone, mirtazapine, physostigmine and nasal lubricants, seem to reduce the number of apneas, but the trials were small and had methodological limitations, precluding the use of these drugs in clinical practice [15]. It has been suggested that drug therapy must be tailored to the mechanism of OSA identified in each patient [15].

An extravascular fluid shift has been implicated in the physiopathology of OSA. During the night, a shift of fluids from the legs causes an increase in neck circumference, peripharyngeal pressure and upper airway collapsibility [16-19]. Almost 60 years ago an increase of 0.5 cm in the size of the earlobes during sleep was described [20]. The application of lower body pressure of 40 mmHg using antishock trousers reduces leg fluid volume and increases neck circumference and the resistance of the pharynx [18].

Patients with controlled hypertension underwent a reduction of 175 mL in leg volume and an increase of 1.0 cm in neck circumference after sleeping, in comparison with a leg volume reduction of 346.7 mL and an increase in the neck circumference of 1.5 cm in patients with resistant hypertension [21]. The leg volume shift is positively correlated to the number of apneas ($R^2 = 0.56$) [21]. CPAP reduced the increase in neck size proportional to the reduction in the number of apneas, but it did not prevent the leg volume change [19].

Sympathetic renal ablation with radio-frequency waves reduced blood pressure by 33/11 mmHg in 6 months [22]. It also reduced the number of apneas/hour from 16.3 to 4.5 for ten patients with resistant hypertension and OSA [23], an effect that was attributed to the promotion of salt excretion and total body fluid reduction [23]. Spironolactone led to a reduction from 39.8 to 22.0 apneas/hour after 8 weeks of treatment of 12 patients with resistant hypertension [24]. There is no controlled study exploring the concept that these drugs may act through total body fluid reduction.

In the ALLHAT trial, chlorthalidone, lisinopril and amlodipine had comparable efficacy in the prevention of coronary heart disease [25]. The diuretic, however, was superior to lisinopril in the prevention of strokes and amlodipine in the prevention of heart failure [25]. There is evidence that the efficacy in the prevention of events is related to the magnitude of the blood pressure reduction [25,26].

The main adverse event for chlorthalidone is hypokalemia, which blunted the efficacy of the treatment in the SHEP trial [27] and increased serum glucose levels [28]. The use of amiloride, a physiological aldosterone antagonist, could ameliorate this adverse effect. This potassium-sparing diuretic was effective and well tolerated in a randomized trial performed by our group [29].

Amlodipine was more effective than valsartan, an angiotensin receptor blocker, in the prevention of myocardial infarction and stroke in the VALUE trial [30]. In the ACCOMPLISH trial, the combination benazepril-amlodipine was more effective in the prevention of composite cardiovascular events than the combination benazepril-hydrochlorothiazide [31]. There is no evidence that amlodipine influences the balance of fluids, and edema is one of its main adverse effects.

Overall the evidence shows that chlorthalidone and amlodipine are the most effective drugs for the initial treatment of hypertension. Their use in OSA has not been appropriately tested to date. Thus, a trial testing the efficacy of these drugs to control both blood pressure and sleep apnea is warranted. Such a trial could contribute to our understanding of the relation between hypertension, fluid levels, hypoxia and OSA.

Rationale

OSA has been associated with fluid retention, which accumulates in the pharynx facilitating its collapse, generating intermittent hypoxia and increasing sympathetic activity and blood pressure. CPAP alleviates apnea, which reduces sympathetic activity, reducing blood pressure and increasing salt and water excretion. Sympathetic renal ablation promotes salt and water excretion, reducing systemic sympathetic activity and total body water (including the pharynx), thus alleviating apnea. Diuretics could be a new way to abort this vicious cycle by promoting the direct excretion of salt and water.

Research question

Is chlorthalidone with amiloride effective in the treatment of OSA in comparison to amlodipine in patients with OSA and hypertension?

Methods/design

This is a randomized double-blind clinical trial, controlled by an active treatment.

Eligible participants

Eligible participants are patients older than 40 years of age with stage I hypertension (140 to 159/90 to 99 mmHg) and moderate OSA (15 to 30 apneas/hour of sleep).

Exclusion criteria

Patients are excluded if they have a low life expectancy, other indications for the use of diuretics or calcium channel blockers, intolerance or contraindications to the study drugs, cardiovascular disease (heart failure or recent – within three months – myocardial infarction or stroke), secondary hypertension or participated in another clinical

trial in the previous 6 months or if they are pregnant or use more than one drug for hypertension.

Random allocation

Randomization will be done using a list generated by validated software (a random allocator), with a block size of four.

Interventions

The interventions are chlorthalidone plus amiloride 25 mg and 5 mg daily, respectively, versus amlodipine 10 mg daily, taken in the morning.

Outcomes

Primary outcomes

1. Number of apneas/hour (apnea-hypopnea index)
2. Blood pressure

Secondary outcomes

1. Adverse events
2. Somnolence scale (Epworth)
3. Respiratory parameters
4. C reactive protein

Follow-up and duration of the study

There will be outpatient clinical visits for evaluation at enrollment and week 8 of treatment. Figure 1 is a flow chart for the selection, interventions, follow-up and outcomes.

Assessment of outcomes

The number of apneas/hour will be measured at the baseline and follow-up by type III portable polysomnography (Somnocheck, Weinmann GmbH, Hamburg, Germany), which was validated by us [10]. Average blood pressure (two measurements using a validated automatic electronic device) and ambulatory blood pressure (Spacelabs 90207, Spacelabs, Redmond, WA) will be measured at the baseline and follow-up.

Sleepiness will be measured using the Epworth somnolence scale at the baseline and follow-up. It records the likelihood that someone will fall sleep during eight daily activities (sitting and reading, watching television, sitting in a public space, being passenger in a car for 1 hour, lying down in the afternoon, sitting and talking to someone, sitting after a meal without alcohol and stopped in a car for few minutes).

Adverse events will be investigated using open questions and a semi-structured questionnaire, with questions on general symptoms and the presumed adverse effects of the drugs used in the trial. Standard laboratory tests will be used to identify adverse events, such as hypokalemia and elevated glucose levels. C-reactive protein levels will be determined as well.

Wash-out

Patients taking an antihypertensive drug will need to stop it for 2 weeks prior to the study to be confirmed for eligibility, to allow time for most of the effects of the blood pressure drug to vanish [32].

Control of adherence

Adherence will be check by counting pills.

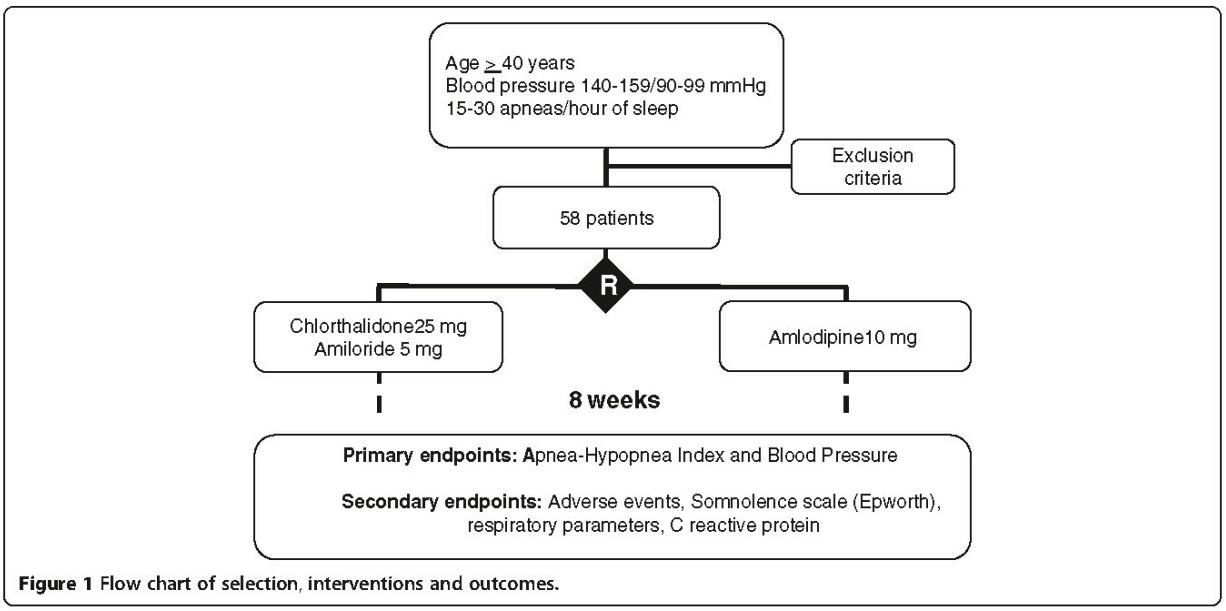

Figure 1 Flow chart of selection, interventions and outcomes.

Sample size calculation

For a mean of 20 apneas/hour at the baseline and a reduction of 7 apneas/hour, with a standard deviation of 9 apneas/hour, power of 80% and P alpha of 5%, 26 patients will be required per group. The sample will be increased by 10% to account for possible losses in follow-up, so that 58 patients need to be randomized.

Statistics

Differences between variables for the groups will be analyzed with chi-squared tests for categorical and Student's t tests for continuous variables. Confounding will be controlled with logistic regression and multiple linear regression models.

Ethical approval

The project and the informed consent form were approved by the ethics committee of the Hospital de Clínicas de Porto Alegre, which is accredited by the Office of Human Research Protections as an Institutional Review Board. All participants will be asked to sign the informed consent form prior to participation in the study.

Trial status

The trial is currently recruiting patients.

Abbreviations

CPAP: Continuous positive airway pressure; OSA: Obstructive sleep apnea.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

FTC conceived the study, revised the background, prepared the data collection plan and prepared the draft of the manuscript. DM participated in the revision of the background, participated in preparing the data collection plan and contributed to drafting the manuscript. SCF participated in preparing the data collection plan and contributed to drafting the manuscript. MG participated in the revision of the background, and revised the draft of the manuscript. LBM participated in preparing the data collection plan and revised the draft of the manuscript. FDF conceived the study, participated in preparing the data collection plan and prepared the final version of the manuscript. All authors read and approved the final version of the manuscript.

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8. ARTIGO 2

Effect of antihypertensive agents on sleep apnea: results from Diuretics Over Sleep Apnea (DOSA) randomized controlled trial.

Cichelero FT, Fuchs SC, Jorge JA, Martinez D, Oliveira GP, Lucca MB, Oliveira ACT, Fuchs FD.

ABSTRACT

Background

Obstructive sleep apnea (OSA) and hypertension are common and associated with increased cardiovascular risk. Both diseases seen to be linked through sympathetic activation and water retention. There is low to moderate quality evidence that reducing fluid retention could improve OSA. We explored the hypothesis that diuretics, which reduce the body water content, are more efficacious than amlodipine, a blood pressure-lowering agent implicated with edema, to control OSA in patients with hypertension.

Methods

In a randomized double-blind clinical trial, we compared the effects of chlorthalidone/amiloride 25/5mg (C) with amlodipine 10mg (A) on sleep apnea measured by portable sleep monitor and blood pressures measured by ambulatory blood pressure monitoring (ABPM). Patients had to be older than 40 years of age with stage I hypertension (140 to 159/90 to 99 mmHg) and moderate OSA (10 to 40 apneas/hour of sleep). The primary outcomes were the number of apneas per hour (AHI) and blood pressure (BP) variation after 8 weeks of treatment.

Results

Patients randomized to diuretics and amlodipine were similar concerning age, sex distribution and other characteristics. There was no difference in the variation of AHI after eight weeks (C 26.1 versus A 24.1, P=0.578). There was no difference in 24 systolic (C 122.2 versus A 125.3, P=0.184) or diastolic (C 76.4 versus A 77.6, P=0.244) BP. There was a reduction of the AHI in the pre-specified subgroup of severe patients of 12.3 events/h (95% CI: 2.0-22.7, P=0.028), without difference between groups.

Conclusions

Chlortalidone/amiloride and amlodipine have no effect over AHI in patients with moderate OSA, and have similar blood pressure-lowering efficacy in a short term observation.

Study registered at clinicaltrials.gov (NCT01896661)

INTRODUCTION

One out of three individuals has Obstructive Sleep Apnea (OSA) or hypertension, and sometimes both conditions (1, 2). OSA is associated with increased cardiovascular risk through several mechanisms, being hypertension one of them (3). Although hypertension treatment is highly effective reducing cardiovascular diseases (4), data in pharmacological treatment of OSA is lacking (5). Indeed, even the diagnosis of OSA is often missed, being neglected in the past (6). OSA should be considered a cardiovascular disease to increase its awareness and treatment (7).

The rationale behind using antihypertensive agents to treat sleep apnea is explained in detail elsewhere (8). Briefly, OSA causes hypoxemia, which leads to sympathetic activation and, water and sodium retention. The accumulation of fluids in the upper airways during sleep is a proposed mechanism of OSA (9). The use of antihypertensive drugs, particularly diuretics, could interrupt this circle, potentially reducing the number and intensity of sleep apneas. The rationale for comparison with amlodipine, an effective blood pressure-lowering agent, is that it is associated with the induction of leg edema, which could be displaced to the upper airway, and therefore being less efficacious to diminish sleep apneas.

Case series and three small randomized clinical trials are the best available evidence of the beneficial effects of diuretics in patients with OSA. The case series studied mainly spironolactone, showing reduction in 10 to 18 apneas per sleep hour (10-13). Two

clinical trials with diuretics were positive, with similar findings, but one wasn't blinded (14) and the other had very short follow-up (15). The third trial tested four classes of antihypertensive agents with small effects (16). In these context we designed the Diuretics Over Sleep Apnea (DOSA) trial, a randomized clinical trial to compare chlortalidone/amiloride with amlodipine to treat OSA in patients with hypertension.

METHODS

Study Design and Oversight

DOSA was a single-center, randomized, double-blind, parallel-group trial. Patients were included from December 1, 2014 through December 4, 2015 in the Clinical Investigation Center of the Hospital de Clínicas de Porto Alegre (HCPA). Participants and investigators were blinded to the study drugs allocation. The trial was approved by the ethics committee of the HCPA (12-0417), which is accredited by the Office of Human Research Protections as an Institutional Review Board (IRB0000921). It was registered in clinicaltrials.gov (NCT01896661) and its protocol was published elsewhere (8).

Study Population

Patients with stage I hypertension (140 to 159 / 90 to 99mmHg) and OSA without treatment (10 to 40 apneas/hour of sleep) were eligible to inclusion if they weren't using pharmacological treatment for hypertension or were using a single drug that could be stopped two weeks before randomization. Among exclusion criteria were indication or contraindication for the study drug, low life expectancy, cardiovascular disease (myocardial infarction or stroke) in the last 3 months, heart failure, secondary hypertension, pregnancy or participation in another clinical trial in the last 6 months.

Treatment

The two study drugs were identical in size, shape, color, taste, and texture. We added amiloride in the same pill of chlortalidone to prevent hypokalemia, a well know side effect of thiazide diuretics (17). After randomization, the patients used a pill of chlortalidone plus amiloride with 25mg and 5mg, respectively, or amlodipine 10mg for 8 weeks, both administered in the morning.

Endpoints

The primary outcome was the number of apneas/hour (apnea-hypopnea index, i.e. AHI) at the eight week. The co-primary outcome was blood pressure (BP). Secondary pre-specified outcomes were adverse effects (open questions), high sensitivity C reactive protein (hsCRP) (immunoturbidimetric assay) and N-terminal pro b-type natriuretic peptide (NT-proBNP) (electrochemiluminescent immunoassay). It was also performed full body bioelectrical impedance with InBody 230 (18) to estimate full body water.

All patients performed an overnight, in laboratory, polysomnography to confirm the diagnosis of OSA. To confirm inclusion criteria, the patients performed a validated (19) home portable polysomnography with Somnocheck device (Weinmann, Hamburg, Germany). The main outcome of the study was the eight-week AHI in portable polysomnography. The portable polysomnography interpretation was performed by two independent evaluators (FTC and ACTO), who were unaware of the treatment or if the exam was done at baseline or at the final evaluation.

The clinic BP was measured 4 times in 2 days, at the beginning and at the end of the study, with an automated device (Microlife BP 3BTO-A, Micromed, Brasilia, Brazil). The 24-hour BP was measured with 15 minutes' intervals during the day and 20 minutes' intervals

during the night, in a different day of the polysomnography, with an oscillometric device (Ambulo 2400, Mortara, Milwaukee, United States of America).

Anthropometric and laboratory measurements, including serum potassium, uric acid, creatinine, urea, fasting glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, hsCRP and NT-proBNP levels were done at baseline and at final visit. Study data were collected and managed using REDCap electronic data capture tools (20) hosted at HCPA.

Sample Size

It was estimated a mean of 20 apneas/hour at the baseline and a reduction of 7 apneas/hour for a minimally relevant clinical effect. Considering a standard deviation of 9 apneas/hour, power of 80% and P alpha of 5%, 26 patients were required per study arm.

Randomization

Randomization was based on a computer-generated list, with variable block sizes and was stratified by sex and OSA severity (AHI 10 to 25 and 26 to 40). To guarantee concealment of the allocation list, randomization was implemented through a web-based automated system.

Statistical Analysis

Trial results were analyzed using the intention-to-treat approach. Data are presented as means and standard deviation when applicable. The continuous and categorical comparisons were performed using respectively independent samples T test and Fisher exact test. When normality wasn’t achieved, the Mann-Whitney U test was used. The within group differences at follow-up were tested by a paired T test. Between groups differences were tested by independent samples T test. The AHI analysis was repeated with

stratification by sex and OSA severity. All analyses were performed with SPSS, version 21.0 (IBM Corporation, North Castle, United States of America).

RESULTS

Between June 2014 and November 2015, a total of 4238 records at a single sleep clinic were screened to identify 864 patients (20%), who were invited to join this trial. Following initial screening, 146 patients accepted to be further evaluated by phone for possible participation in DOSA trial, ending with 118 patients who attended consultations between December 2014 and December 2015. After home portable polysomnography, 53 patients (45%) met the inclusion criteria and were randomized. The reasons for no participation in the trial were detailed in study flow-chart (Figure 1). After eight weeks, three patients were lost in the follow-up (5.6%): 2 patients in amlodipine group failed to attend the follow up consultation and withdraw consent and 1 patient in chlortalidone/amiloride group moved to other city and could not perform the final home polysomnography.

Baseline characteristics of the randomized participants were similar between groups (Table 1). Mean age was 54 years, approximately two-thirds were men, and had around 14 years of education. Less than 30% knew they had hypertension and three-quarter of them were using BP lowering drugs and performed washout according to protocol. The mean baseline AHI were 25 apneas or hypopneas per hour of sleep.

Table 2 shows that AHI did not change in patients treated with diuretic or amlodipine. The blood lowering effects were similar for both drugs. The laboratorial (Table 3) and anthropometric (Table 4) outcomes also were similar by treatment arms. Both treatments decreased potassium in 0.2mEq/L ($P<0.05$), without differences between group ($P=0.776$). There was a trend toward glucose reduction for diuretic group (-2.9mg/dL, 95% confidence interval -6.3 to +0.5, $P=0.095$), without differences between groups ($P=0.799$). Total body

water was not different by treatment (42.7 versus 42.5L, in the diuretic and amlodipine arms, respectively, P=0.967).

Adverse events were reported by 35% of the patients, without any difference between groups (Table 5). Lower limb edema was the most common complaint. Adherence to treatments was satisfactory and not different by treatment (P=0.802), with median Morisky scale 1 for both groups, with interquartile ranges 1.63 for Chlortalidone/Amiloride and 1.13 for Amlodipine.

The pre-specified subgroups for AHI are showed in Table 6. There weren't any differences between groups. Patient with severe OSA had a reduction of 12.3 events/h after trial (95% Confidence Interval 2.0-22.7, P=0.028).

DISCUSSION

This trial showed that two drugs commonly employed in the management of hypertension had no effect on OSA. The similar blood pressure-lowering effect was expected and not different by treatment arms. Adverse events and a long list of putative intermediate parameters and laboratorial outcomes were not influenced by treatment with chlorthalidone/amiloride or amlodipine.

The findings from a randomized crossover trial are in accordance with our study (16). Amlodipine, enalapril and hydrochlorothiazide, promoted very small decreasing in AHI in patients with high indexes at baseline, while losartan increased the number of events. A very short randomized, parallel study (one week) showed small decrease of AHI in an intensive low salt diet and with an association of furosemide and spironolactone (15). Case series (11, 12, 14, 15) are hypothesis generating, since they do not control for regression to the mean and placebo effect. The proposition that ACE inhibitors could be ineffective due to the induction of cough is speculative (13, 21).

Our hypothesis that the association of diuretics could have higher effect over OSA than amlodipine due to different effects over total body fluids and its displacement to upper airway was not confirmed. The possibility of a beta error is unlikely, since there was no trend towards a beneficial effect of diuretics. Total body water and the incidence of limb edema did not differ by treatment group as well, suggesting that the dose of diuretic did not promote a substantial change in the body fluid content. The possibility that other diuretics, such as spironolactone, with other mechanisms of action, are effective should be addressed in randomized controlled trials adequately powered.

The similar effect of chlorthalidone with amiloride and of amlodipine over ambulatory blood pressure was expected with this sample size. In the ALLHAT trial (22), chlorthalidone alone had higher effect in systolic and lower effect in diastolic blood pressure than amlodipine, but more than 15.000 individuals were studied. The effects over laboratorial parameters and the incidence of adverse events confirmed the safety of these traditional blood pressure lowering drugs.

In conclusion, chlorthalidone with amiloride and amlodipine are ineffective to lower sleep apnea in patients with moderate OSA. The lack of effect of an association of chlorthalidone with a physiological antagonist of aldosterone suggests that putative effect of spironolactone shown in uncontrolled studies should be confirmed in randomized, parallel, clinical trials.

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DISCLOSURES

All of the authors reported they had no conflicts of interest and financial disclosures concerning the subject of this manuscript.

FIGURE AND TABLES

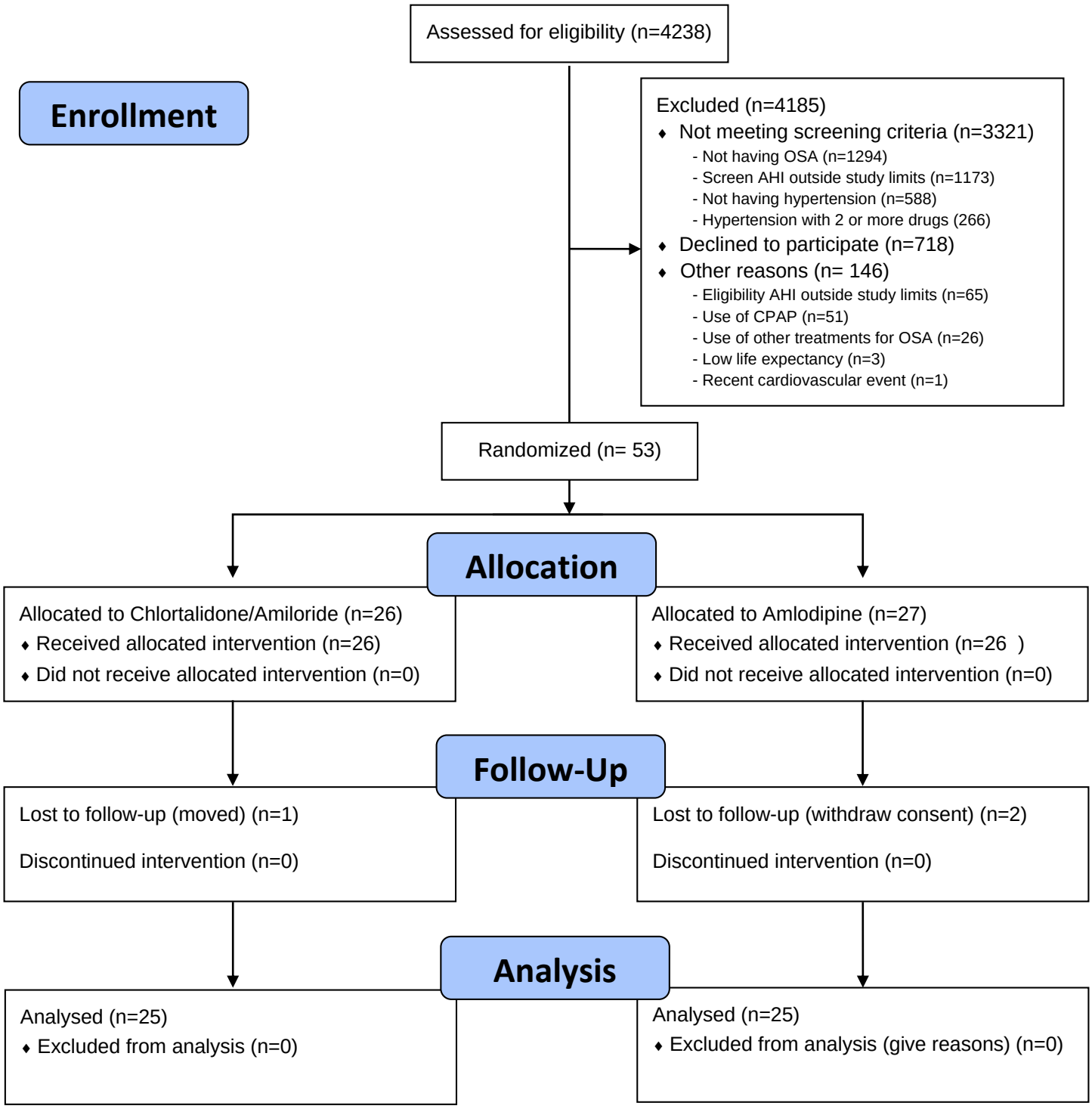

Figure 1. Study flow diagram (OSA: Obstructive Sleep Apnea; AHI: Apnea Hypopnea Index; CPAP: Continuous Positive Airway Pressure).

Table 1. Baseline characteristics (BMI: Body Mass Index).

	Chlortalidone/Amiloride (n=26)	Amlodipine (n=27)	P
Age - yr	53.1 ± 7.6	55.1 ± 7.7	0.34
Sex - no. (%)			1.00
Male	17 (65)	17 (63)	
Female	9 (35)	10 (37)	
Education - yr	14.8 ± 3.5	13.7 ± 3.8	0.32
Weight (Kg)	86.9 ± 17.1	85.4 ± 12.5	0.71
BMI (Kg/m²)	29.0 ± 3.8	29.8 ± 3.6	0.45
Office Blood Pressure (mmHg)			
Systolic	127.9 ± 10.1	131.5 ± 10.8	0.22
Diastolic	85.5 ± 7.2	84.4 ± 6.4	0.57
Ambulatory Blood Pressure (mmHg)			
Daytime Systolic	134.6 ± 11.0	140.6 ± 10.0	0.05
Nighttime Systolic	122.2 ± 15.9	127.8 ± 16.7	0.24
24h Systolic	130.3 ± 11.5	136.5 ± 11.2	0.06
Daytime Diastolic	83.5 ± 5.4	85.0 ± 6.2	0.39
Nighttime Diastolic	74.8 ± 6.7	76.5 ± 7.1	0.40
24h Diastolic	80.7 ± 5.6	82.4 ± 5.5	0.29
Apnea-Hypopnea Index (events/hour)	26.7 ± 10.2	24.4 ± 8.2	0.38
Medical History - no. (%)			
Hypertension	6 (23)	9 (33)	0.54
Use of BP lowering drugs	4 (15)	7 (26)	0.50
Diabetes Mellitus	1 (4)	4 (16)	0.14
Myocardial Infarction	0 (0)	1 (4)	0.49
Past Smoker	5(19)	6 (24)	0.74
Actual Smoker	2 (8)	1 (4)	0.61
Medication use - no. (%)			
Metformin	1 (4)	4 (16)	0.35
Glyburide	0	1 (4)	1.00
Tricyclic antidepressant	1 (4)	1 (4)	1.00
Serotonin Reuptake Inhibitor	9 (35)	9 (35)	1.00
Benzodiazepines	3 (12)	0	0.23
Nonsteroidal Anti Inflammatory	0	1 (4)	1.00
Corticosteroid	0	1 (4)	1.00
Statin	4 (15)	4 (15)	1.00

Table 2. Main Outcomes (CI: Confidence Interval).

	Basal	Final	Within group P value	Between group P value
Apnea-Hypopnea Index (events/hour)				
Chlortalidone/Amiloride	26.9	26.1	0.730	0.578
Amlodipine	24.4	24.1	0.891	
Office Systolic Blood Pressure (mmHg)				
Chlortalidone/Amiloride	127.9	122.4	0.009	0.644
Amlodipine	130.6	121.2	<0.001	
Office Diastolic Blood Pressure (mmHg)				
Chlortalidone/Amiloride	85.5	80.4	<0.001	0.577
Amlodipine	83.8	79.4	<0.001	
Daytime Systolic (mmHg)				
Chlortalidone/Amiloride	135.2	127.0	0.010	0.243
Amlodipine	139.9	129.6	<0.001	
Nighttime Systolic (mmHg)				
Chlortalidone/Amiloride	122.9	112.1	0.002	0.154
Amlodipine	126.4	117.3	0.045	
24h Systolic (mmHg)				
Chlortalidone/Amiloride	131.0	122.2	0.004	0.184
Amlodipine	135.6	125.3	0.002	
Daytime Diastolic (mmHg)				
Chlortalidone/Amiloride	83.5	78.7	0.003	0.158
Amlodipine	84.9	80.2	0.002	
Nighttime Diastolic (mmHg)				
Chlortalidone/Amiloride	75.0	71.3	0.012	0.478
Amlodipine	75.7	72.6	0.063	
24h Diastolic (mmHg)				
Chlortalidone/Amiloride	80.8	76.4	0.005	0.244
Amlodipine	82.0	77.6	0.001	

Table 3. Laboratorial Outcomes (CI: Confidence Interval).

	Basal	Final	Within group P value	Between group P value
Total Cholesterol (mg/dL)				
Chlortalidone/Amiloride	207.4	209.2	0.780	0.397
Amlodipine	202.2	202.4	0.966	
HDL Cholesterol (mg/dL)				
Chlortalidone/Amiloride	46.7	48.1	0.267	0.682
Amlodipine	48.0	49.3	0.330	
Triglycerides (mg/dL)				
Chlortalidone/Amiloride	153.5	146.0	0.629	0.223
Amlodipine	147.6	123.0	0.200	
Glucose (mg/dL)				
Chlortalidone/Amiloride	98.4	95.6	0.095	0.799
Amlodipine	92.8	94.4	0.327	
Potassium (mEq/L)				
Chlortalidone/Amiloride	4.6	4.4	0.041	0.776
Amlodipine	4.6	4.4	0.015	
Uric Acid (mg/dL)				
Chlortalidone/Amiloride	5.4	6.1	0.014	0.540
Amlodipine	5.4	5.8	0.091	
Creatinine (mg/dL)				
Chlortalidone/Amiloride	0.86	0.88	0.462	0.516
Amlodipine	0.87	0.85	0.234	
Urea (mg/dL)				
Chlortalidone/Amiloride	32.8	35.6	0.098	0.530
Amlodipine	35.6	37.0	0.408	
Pro-BNP (pg/mL)				
Chlortalidone/Amiloride	31.0	25.8	0.338	0.416
Amlodipine	41.0	34.3	0.231	
hs-CRP (mg/L)				
Chlortalidone/Amiloride	2.8	2.8	0.929	0.977
Amlodipine	1.8	2.8	0.126	

Table 4. Anthropometric Outcomes (CI: Confidence Interval).

	Basal	Final	Within group P value	Between group P value
BMI (Kg/m²)				
Chlortalidone/Amiloride	29.0	28.9	0.175	0.367
Amlodipine	29.7	29.5	0.086	
Weight (Kg)				
Chlortalidone/Amiloride	87.0	86.5	0.206	0.559
Amlodipine	85.9	85.3	0.100	
Neck circumference (cm)				
Chlortalidone/Amiloride	39.8	40.0	0.723	0.374
Amlodipine	40.7	40.9	0.523	
Total Body Water (L)				
Chlortalidone/Amiloride	43.4	42.7	0.027	0.967
Amlodipine	43.4	42.5	0.360	

Table 5. Adverse events - no. (%). Two patients in Chlortalidone/Amiloride had 3 adverse events and 1 patient in Amlodipine group had 2 adverse events.

	Chlortalidone/Amiloride n=26	**Amlodipine n=25**	**P**
Any adverse event*	8 (30)	10 (40)	0.565
Lower limb edema	7 (26.9)	8 (32.0)	0.764
Generalized edema	1 (3.8)	1 (4)	1.000
Dizziness	0	2 (8)	0.235
Cramps	1 (3.8)	0	1.000
Headache	1 (3.8)	0	1.000
Pain	2 (7.7)	0	0.490

Table 6. Apnea-Hypopnea Index according to pre-specified subgroups (CI: Confidence Interval).

Apnea-Hypopnea Index (events/hour)	Basal	Final	Within group P value	Between group P value
Men (n=33)				
Chlortalidone/Amiloride	28.9	29.6	0.813	0.520
Amlodipine	25.6	26.5	0.740	
Women (n=17)				
Chlortalidone/Amiloride	23.5	19.9	0.460	0.819
Amlodipine	21.9	18.7	0.528	
Moderate OSA (n=44)				
Chlortalidone/Amiloride	23.4	24.5	0.674	0.799
Amlodipine	22.6	23.5	0.714	
Severe OSA (n=6)				
Chlortalidone/Amiloride	45.5	34.2	0.082	0.728
Amlodipine	44.5	30.0	0.413	

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9. CONCLUSÕES

Esse ensaio clínico randomizado demonstrou, com razoável grau de certeza, que clortalidona/amiloridaouanlodipino não são efetivos no tratamento de SAHOS moderada. Existem duas hipóteses que podem ser levantadas. A primeira é que possivelmente seja necessário diureticoterapia mais intensa, provavelmente incluindo espironolactona, para um efeito que seja clinicamente significativo na redução de apneias. Em segundo lugar, é possível que apenas pacientes com SAHOS mais grave sofram de forma mais significativo do efeito da redistribuição cranial de fluídos, sendo restrito o benefício a estes pacientes.

O fato de apenas os pacientes mais graves terem respondido pode se dever a erro alfa, já que se constitui de análise de subgrupo com pequeno número de observações. Entretanto, se verdadeira essa diferença, corrobora com as duas novas hipóteses, merecendo ser apropriadamente testada em novo ensaio clínico randomizado. Um desenho possível seria a comparação de anlodipino com espironolactona em hipertensos com SAHOS grave, respondendo ao mesmo tempo sobre os efeitos anti-hipertensivos e redutores dos fluídos corporais e suas relações com o número de apneias. Talvez fosse interessante incluir um grupo placebo para melhor controle do possível efeito de regressão à média, que pode ser intensificado se estudados pacientes mais graves.

Por fim, este foi um ensaio clínico randomizado que refutou a hipótese de que clortalidona/amiloridaouanlodipino poderiam reduzir o número de apneias do sono. Houve semelhante benefício anti-hipertensivo, além de equivalente tolerabilidade clínica e laboratorial.