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Revisões Sistemáticas e Meta-análises de estudos de Acurácia do teste da desmopressina na síndrome de Cushing

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

Orientadora: Profa. Dra. Vania dos Santos Nunes Nogueira.

Botucatu

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Palavras-chave: desmopressina; doença de Cushing; pseudo-Cushing; síndrome de Cushing; síndrome do ACTH ectópico.

Dedicatória

À minha família, pelo apoio em todas conquistas.

Epígrafe

"Há pessoas que desejam saber só por saber, e isso é curiosidade; outras, para alcançarem a fama, e isso é vaidade; outras, para enriquecerem com a sua ciência, e isso é um negócio torpe; outras, para serem edificadas e isso é prudência; outras, para edificarem os outros, e isso é caridade"

Santo Agostinho

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LISTA DE ABREVIAÇÕES

ACTH: hormônio adrenocorticotrófico

AUC: *area under the curve*

AVPR1B: *arginine vasopressin receptor 1 B*

AVPR2: *arginine vasopressin receptor 2*

BBO: Bibliografia Brasileira de Odontologia

BDENF: Base de Dados Enfermagem

BVS: Biblioteca Virtual da Saúde

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CD: *Cushing disease*

CENTRAL: *Cochrane Controlled Register of Trials*

CG: *control group*

CI: *confidence interval*

CINAHL: *Cumulative Index to Nursing and Allied Health Literature*

CMT*:* carcinoma medular de tireóide

CPPC*:* carcinoma pulmonar de pequenas células

CRDTAS: *Cochrane* Register of Diagnostic Test Accuracy Studies

CRH: hormônio liberador de corticotrofina

CS: *Cushing syndrome*

DC: doença de Cushing

dOR: acurácia global

dOR: *diagnostic odds ratio*

DPC: Diagnostic Products Corporation

DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders III - Review*

DST: teste de supressão com dexametasona

DTA: *diagnostic test accuracy*

E: especificidade

EAS*: ectopic ACTH syndrome*

Embase: Excerpta Medica dataBASE

ev: endovenoso

FAPESP: Fundação de Amparo à Pesquisa do Estado de São Paulo

FP: falso positivo

GC: grupo controle

hCRH: hormônio liberador de corticotrofina humano

I: teste índice

$I^{2:}$ teste de Higgins

IBECS: Índice Bibliográfico Espanhol de Ciências de Saúde

IC: intervalo de confiança

IC: intervalo de confiança

INCA: Instituto Nacional de Câncer

LDDST: teste de supressão com dose baixa de dexametasona

LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde

LR -: razão de verossimilhança negativa

LR + : razão de verossimilhança positiva

lsn: limite superior da normalidade

MEDCARIB: Literatura em Ciências da Saúde dos países do Caribe

N: número de participantes na amostra

NETs: *neuroendocrine tumours*

O: *outcome*

oCRH: hormônio liberador de corticotrofina ovino

P: população

PC: pseudo-Cushing

PCDT: Protocolos Clínicos e Diretrizes Terapêuticas

POMC: pro-opiomelanocortina

PRISMA: Principais Ítens para Relatar Revisões sistemáticas e Meta-análises

QUADAS-2: *Quality Assessment of Diagnostic Accuracy Studies*

R: teste referência

ReBEC: Registro Brasileiro De Ensaios Clínicos

RIA: radioimunoensaio

RNM: ressonância magnética

RV -: razão de verossimilhança negativa

RV +: razão de verossimilhança positiva

S: sensibilidade

SAE: síndrome do ACTH ectópico

SC: síndrome de Cushing

SOP: síndrome dos ovários policísticos

sROC: *Summary Receiver Operator Curve*

UFC: cortisol livre urinário

UK: Reino Unido

USA: Estados Unidos da América

USP: Universidade de São Paulo

VP: verdadeiro positivo

V1b: receptor da vasopressina 1 B

V2: receptor da vasopressina 2

V3: receptor da vasopressina 3

RESUMO

Este estudo objetivou avaliar a acurácia do teste da desmopressina em diferenciar doença de Cushing (DC) da síndrome do ACTH ectópico (SAE) e da síndrome de pseudo-Cushing (PC), através de duas revisões sistemáticas de estudos da acurácia de teste diagnóstico (DTA) nos quais pacientes com DC e SAE ou com DC e PC foram submetidos ao teste da desmopressina. As bases de dados LILACS, PubMed, EMBASE, e CENTRAL Cochrane foram pesquisadas. Dois revisores, independentemente, avaliaram os estudos em relação à eligibilidade, risco de viés e extraíram os dados. As meta-análises utilizaram os modelos bivariado ou *hierarchical summary receiver operating characteristic* (HSROC). A qualidade da evidência foi obtida de acordo com os critérios do GRADE *(Grading of Recommendations Assessment, Development and Evaluation Working Group)*. Cinco estudos de DTA incluídos na revisão sistemática e meta-análise de DC e PC totalizaram 203 pacientes; a maioria deles apresentava hipercortisolismo leve. Com baixa certeza na evidência, a sensibilidade combinada para o diagnóstico de DC foi 89 % (95% Intervalo de Confiança (IC), 81%-94%) e a especificidade 93% (95% IC, 87%-97%). A acurácia diagnóstica obtida pela *symmetric summary receiver-operator characteristic* (curva ROC) foi 0.96 (95% IC, 0.94 - 0.98). A análise univariada por subgrupos em relação a uma elevação do hormônio adrenocorticotrófico > 4 pmol/L associado a um cortisol basal > 331 nmol/L vs. ACTH > 6 pmol/L resultou em sensibilidade e especificidade de 93 % (83-98 %) vs. 85 % (70-94 %) e de 94 % (83-99%) vs. 94 % (84-99 %), respectivamente, sem diferença estatística. Oito estudos DTAs tiveram 345 indivíduos incluídos na revisão sistemática entre DC e SAE; sete estudos (331 participantes) utilizaram uma elevação percentual no ACTH (Δ%) e sete (175 participantes) utilizaram um Δ% cortisol. A sensibilidade sumária para o diagnóstico de DC foi de 0.83 (95% Intervalo de confiança (IC), 0.78-0.87) para o Δ% ACTH e de 0.80 (95% IC, 0.72-0.85) para o Δ% cortisol. Em ambas análises, o intervalo preditivo 95% (IP) não foi próximo ao IC e 17% (15%-28%) dos portadores de DC seriam perdidos no teste da desmopressina. Contudo, para especificidade em relação ao Δ% ACTH e cortisol, as análises demonstraram elevada heterogeneidade entre os estudos através da análise da *hierarchical summary ROC curve plot* (IP distante do IC) e pelo resultado obtido no Stata (0.62 (IC, 0.45-0.77) e 0.68 (IC, 0.48-0.83), respectivamente. Apenas um estudo avaliou a sensibilidade e especificidade em relação ao incremente do ACTH associado ao do cortisol, com sensibilidade de 0.65 (IC,0.38-0.86) e especificidade de 0.75 (IC, 0.19 – 0.99). Assim, a especificidade do teste da desmopressina em diferenciar DC de SAE foi heterogênea; apesar

da incerteza em relação à sensibilidade ter sido inferior, nossos resultados sugerem que cerca de 20% daqueles com DC serão perdidos pelo teste. PROSPERO números de registros: CRD42018085634 (PC) e CRD42017068317 (SAE)

Palavras chave: ACTH ectópico, desmopressina, doença de Cushing, pseudo-Cushing, síndrome de Cushing.

ABSTRACT

The aim of this study was to evaluate the accuracy of the desmopressin test to differentiate Cushing's disease (CD) from ectopic ACTH syndrome (EAS) and from Pseudo-Cushing´s syndrome (PCS) For this, two systematic reviews of diagnostic test accuracy (DTA) studies in which patients with CD and ectopic ACTH syndrome or with CD and PCS underwent desmopressin test were realized. The LILACS, PubMed, EMBASE, and CENTRAL Cochrane databases were searched. Two reviewers independently assessed the studies for their eligibility, risk of bias, and extracted data. The meta-analysis used bivariate or hierarchical summary receiver operating characteristic (HSROC) models. The quality of the evidence was generated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation Working Group) criteria. Five included DTAs studies in the systematic review with CD and PCS comprised 203 individuals; most of them had mild hypercortisolism. With low certainty evidence, pooled sensitivity for CD diagnosis was 89 % (95% Confidence Interval (CI), 81%-94%) and the specificity was 93% (95% CI, 87%-97%). The test accuracy obtained by the symmetric summary receiver-operator characteristic (ROC curve) was 0.96 (95% CI, 0.94 - 0.98). The univariate pooled subgroup analysis according to a net (relative) increment in adrenocorticotropic hormone (ACTH) > 4 pmol/L plus a basal serum cortisol > 331 nmol/L vs. ACTH > 6 pmol/L, showed sensitivities and specificities of 93 % (83-98 %) vs. 85 % (70-94 %) and 94 % (83-99%) vs. 94 % (84-99 %), respectively, without statistical differences. We included eight DTAs studies, with 345 individuals in the systematic review of CD vs. EAS; seven studies (331 participants) used an ACTH percent increment (Δ%), and seven (175 participants) used a cortisol Δ%. The pooled sensitivity for CD diagnosis was 0.83 (95% Confidence Interval (CI), 0.78-0.87) for ACTH Δ% and 0.80 (95% CI, 0.72-0.85) for cortisol Δ%. In both analyses, the 95% prediction intervals (PI) were not near the CI and for individuals with CD, 17% (15%-28%) will be missed by the desmopressin test. However, for specificity in regard Δ% ACTH and cortisol, the analyses showed high levels of heterogeneity between studies, which can be seen from both the hierarchical summary ROC curve plot (PI far from CI) and the Stata output (0.62 (CI, 0.45-0.77) and 0.68 (CI, 0.48-0.83), respectively. Only one study evaluated the sensitivity and specificity of a composite rule requiring an ACTH increase and a cortisol increase, whose values were 0.65 (CI,0.38-0.86) and 0.75 (CI, 0.19 – 0.99), respectively. Thus, the specificity of desmopressin test to distinguish CD from EAS has been very heterogeneous. Although the uncertainty in the sensibility is much lower, our results suggest that an average of 20% of CD

diagnosis would be lost by this test. PROSPERO registration numbers: CRD42018085634 (PCS) and CRD42017068317 (EAS)

Keywords: Cushing´s syndrome, Cushing´s disease, pseudo-Cushing, desmopressin, ectopic ACTH syndrome.

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CAPÍTULO 1: REVISÃO DE LITERATURA

1.1 Doença de Cushing

A Síndrome de Cushing é caracterizada pelos sinais e sintomas decorrentes da prolongada exposição a níveis elevados de corticoesteróides, pela perda da regulação do eixo hipotálamo- hipófise- adrenal e pela inconsistência do ritmo circadiano na secreção de cortisol.[1] Tem como causa principal o uso crônico de glicocorticóides, podendo também ser devido a um aumento da produção endógena desses hormônios.[2]

As etiologias da Síndrome de Cushing endógena podem ser genericamente divididas em duas categorias: ACTH dependentes e ACTH independentes.[3] As etiologias ACTH dependentes são decorrentes da produção inadequada de ACTH enquanto as ACTH independentes, que cursam com níveis diminuídos de ACTH, são decorrentes de uma doença primária da adrenal, como adenomas, carcinomas, hiperplasias macronodulares primárias, doença adrenal nodular pigmentar primária ou mesmo Síndrome de McCune Albright.[3, 4]

A etiologia mais prevalente de Síndrome de Cushing endógena em adultos é a doença de Cushing, responsável por aproximadamente 70% dos casos dessa síndrome.[2] Esta condição ocorre devido à produção aumentada de ACTH por um adenoma hipofisário e apresenta incidência de 2-3 casos/ 1.000.000 habitantes ao ano e prevalência de 40 casos/ 1.000.000 habitantes, [5] além de maior frequência no sexo feminino (3-8:1) [5, 6]

A síndrome de Cushing é uma desordem incapacitante, em especial devido a suas complicações, como osteoporose, hipertensão não controlada, diabetes mellitus e dislipidemia, levando à uma maior incidência de doenças cardiovasculares, além da presença de alguns transtornos psiquiátricos e hipogonadismo [7–10]. Algumas das manifestações clínicas são: obesidade predominantemente visceral, com atrofia dos membros; pletora facial; fraqueza da musculatura proximal; pele fina; equimoses espontâneas; hirsutismo; calvície; estrias violáceas; irregularidade menstrual nas mulheres. [3, 11]

O diagnóstico de Síndrome de Cushing endógena se inicia pela determinação de um estado de hipercortisolismo e da perda do ritmo circadiano da secreção do cortisol, ambos confirmados pela positividade de pelo menos dois dos seguintes testes: cortisol livre urinário de 24h (UFC); cortisol salivar à meia-noite e supressão com 1 mg de dexametasona noturna (DST 1 mg). [3, 11]

O segundo passo no diagnóstico é determinar se a Síndrome de Cushing é dependente

ou independente de ACTH, que se faz pela medida de duas amostras do ACTH plasmático, adotando-se concentrações plasmáticas superiores a 20 pg/ml para causas dependentes desse hormônio. [11–14]

Além da DC como principal etiologia SC ACTH dependente, [1] ocorrem ainda neoplasias associadas à produção ectópica do ACTH (SAE), correspondendo entre 10 a 20 % das causas de SC ACTH dependente e entre 5-10% dos quadros de SC: [15, 16] tumores neuroendócrinos (NETs) pulmonares, tímicos, pancreáticos; carcinoma pulmonar de pequenas células (CPPC); feocromocitoma, carcinoma medular de tireóide (CMT), entre outros [15–17]; contudo, em até 20 % dos casos a fonte produtora do ACTH pode permanecer oculta [15, 17, 18]

Diferentemente da DC, a SAE incide em pacientes mais velhos [19, 20], tendo distribuição entre mulheres e homens de 0,6-1:1 [4, 15], podendo apresentar quadro clínico mais agressivo a depender do tumor em questão, geralmente mais frequente no CPPCs, em que, além de hiperpigmentação cutânea, pode se associar à hipocalemia, perda de peso e catabolismo [15, 17]. Porém, alguns outros tumores podem apresentar quadro clínico similar ao da DC, sendo difícil apenas pela clínica sua distinção. [15, 17]

Apesar de alguns pacientes com SAE secundária à CPPC apresentarem maiores valores de ACTH plasmático e cortisol sérico, muitos portadores de SAE e DC apresentam sobreposição nos valores desses exames [15, 17, 22], não podendo esses assim serem utilizados da distinção da SC ACTH dependente.

Assim, após a confirmação do hipercortisolismo ACTH dependente, tornam-se necessários exames adicionais, sendo mais frequentemente utilizados o teste do CRH, o exame de supressão do cortisol após dose elevada de dexametasona (HDDST), a ressonância magnética de hipófise e o cateterismo bilateral e simultâneo dos seios petrosos inferiores para distinção entre doença de Cushing (DC) e Síndrome do ACTH Ectópico (SAE). [12, 23–25]

O teste do CRH se justifica pela expressão elevada de receptores do CRH do subtipo 1 na DC, diferentemente do tecido hipofisário sadio [26–28], e consiste na administração do hormônio liberador da corticotrofina humano ou ovino, na dose de 1 µg/kg ou 100 µg, via endovenosa, com dosagem do cortisol sérico e ACTH plasmático após estímulo, tendo como critério de positividade para DC um aumento em relação ao basal de 20 % para o cortisol (sensibilidade 91 %, especificidade 88 %) e de 35 % para o ACTH, (sensibilidade 93 %, especificidade 100 %) quando administrado o hormônio ovino [29], e de 14% para o cortisol (sensibilidade 85 %, especificidade 100 %) e 105 % para o ACTH, (sensibilidade 70 %,

especificidade 100 %) quando administrado o humano. [30] Contudo, dado seu custo e indisponibilidade no Brasil e no mundo, seu uso tem sido cada vez menor. [11]

Quanto ao teste com supressão do cortisol após dose elevada de dexametasona (HDDST), seu uso se justifica pela preservação do *feedback* negativo em pacientes com doença de Cushing. [23, 24] Apesar do baixo custo e boa disponibilidade, apresenta baixa acurácia diagnóstica entre doença de Cushing e síndrome do ACTH ectópico [12, 31] já que entre 5-25 % daqueles com SAE podem apresentar supressão ao teste [15, 17, 32] e até 20 % dos casos de DC podem não apresentá-la. [1,31] O valor previamente adotado para a supressão do cortisol sérico, coletado entre 8 a.m. e 9 a.m. em jejum, após ingestão noturna de 8 mg de dexametasona, seria de 50 % nos quadros de doença de Cushing, com sensibilidade variando entre 60 - 100 % e especificidade entre 65 - 100 %. [33–37] Visando melhorar a especificidade do teste, alguns autores propuseram a supressão em 80 % do cortisol após 8 mg de dexametasona como *cut-off*, [23, 24] apresentando, porém, baixa acurácia [24]

Considerendo-se que os microadenomas hipofisários são responsáveis por aproximadamente 80-90 % dos casos de DC [22, 38, 39] e que incidentalomas hipofisários podem estar presentes em até 10 % da população, [40] os últimos consensos [3, 11] têm recomendado que nos quadros de SC ACTH dependente, a presença de uma lesão hipofisária com diâmetro superior ou igual a 6 mm em exame de ressonância magnética de hipófise quando associada à supressão com dose elevada de dexametasona (HDDST) ou aos critérios considerados no teste com CRH [12, 41, 42] sugere o diagnóstico de DC. [3, 11, 40]

O cateterismo bilateral e simultâneo dos seios petrosos inferiores é considerado "padrão-ouro" na distinção entre SAE e DC, com acurácia diagnóstica entre 90-98 % [14, 43, 44] e deve ser indicado quando ressonância, teste com CRH e HDDST se mostram discordantes. [12, 13, 42, 45–47] É realizado sob estímulo com oCRH, hCRH (1 µg/kg ou 100 µg, via endovenosa) ou desmopressina (10 µg endovenosa), com coletas de ACTH plasmático nos tempos basal, 3, 5 e 10 minutos após estímulo, sendo os gradientes ACTH central/ ACTH periférico > 2 sem estímulo ou > 3, quando do pico do estimulatório induzido por tais medicamentos, considerados pontos de corte para o diagnóstico da DC. [13, 14, 48]

Apesar de ser considerado o teste padrão ouro para diferenciar esses dois diagnósticos, o cateterismo, além de invasivo, tem uma limitada disponibilidade em nosso meio [11] devido à necessidade de profissionais altamente capacitados para fazê-lo [11] e, apesar da baixa incidência reportada por alguns autores, pode apresentar complicações graves, como lesões vasculares cerebrais, tromboembolismo venoso, paralisia dos nervos cranianos e hemorragia

subaracnóidea.[49, 50] Por isso, na maioria das vezes, costuma ser utilizado nas situações que a investigação laboratorial sugere DC, mas a RNM não identifica lesão. [12, 13, 42, 45–47]

Devido à indisponibilidade do CRH, este teste tem sido substituído pelo teste da desmopressina (1-deamino-S-D-arginine vasopressina), [11] que é o análogo sintético do AVP com alta seletividade pelos receptores AVPR2 (V2) renais, onde promove efeito anti-diurético não pressórico [51, 52]; com menor afinidade, nos receptores AVPR1B (V3 ou V1b), produz um aumento na secreção do ACTH e potencialização das ações do CRH nos indivíduos portadores de DC, diferentemente daqueles saudáveis, [28, 53], possivelmente, pela hiper-expressão do receptor V3 ou pela presença de um receptor V2 ectópico nas células tumorais hipofisárias produtoras de ACTH .[53–55]

Após a descrição em 1993 por Malerbi e colaboradores [56] do teste da desmopressina nas diferentes etiologias de SC, obtendo resposta ao teste em 15 de 16 portadores de DC (93,75 %), que se mostrou ausente em dois prováveis portadores de SAE e em um com SAE confirmada, muitos outros autores buscaram empregar o teste da desmopressina para diferenciar a DC da SAE.

Não obstante à dificuldade existente na distinção entre DC e SAE, há um grupo heterogêneo de distúrbios, tanto fisiológicos (como estresse associado à cirurgia, doença grave ou estresse emocional) quanto não fisiológicos (como alcoolismo crônico e síndrome de abstinência, depressão maior, síndrome dos ovários policísticos, obesidade e diabetes mellitus mal controlado) que levam ao aumento da produção de cortisol, bem como às características clínicas e laboratoriais observadas na SC, [1, 57–60] e que apresentam hipercortisolismo leve a moderado dependente de ACTH. [1, 57, 58]

Com a crescente prevalência de tais condições associadas a estados de “pseudo-Cushing” (PC), diferenciá-lo da DC pode ser desafiador [10]. Os testes de triagem usados para diagnosticar a SC, como o teste de supressão com dexametasona, o cortisol livre urinário de 24 horas (UFC) e o cortisol salivar noturno podem ser imprecisos para excluir o diagnóstico de SC nessas situações clínicas [11, 25, 58]. Para se diferenciar DC de PC, testes diagnósticos têm sido utilizados: teste de estímulo com hormônio liberador de corticotropina (CRH) após supressão com dexametasona via oral (teste DEX-CRH) [25, 61–63] e o teste de estímulo com desmopressina. [64] Na publicação original [65], o teste DEX-CRH mostrou 100% de precisão, mas esse achado não foi reproduzido em estudos subsequentes [61–63]. Além disso, devido ao alto custo e indisponibilidade de CRH ovina, seu uso é atualmente limitado. [11] O teste com a desmopressina tem a vantagem de ser barato e ter demonstrado, segundo alguns autores, alta precisão diagnóstica, apesar de diferentes pontos de corte

propostos [56, 64, 66–69]. Quanto ao teste de supressão do cortisol sérico com 2 mg de dexametasona via oral ou fracionada em 48 h, (8 doses de 0,5 mg), sua especificidade encontra-se prejudicada por situações de estresse ou por patologias que alterem o metabolismo da dexametasona [11], tendo aplicabilidade técnica elaborada e acurácia diagnóstica inferior ao teste com 1 mg, conforme demonstrado na meta-análise publicada em 2008 por Elamin e colaboradores, [70] não devendo ser utilizado na distinção entre DC e PC.[11]

Assim, dado que tem se tornado cada vez mais freqüente o surgimento de indivíduos com doenças associadas à PC, [71, 72] considerando-se que o teste de estímulo com desmopressina via endovenosa se mostra exequível na maioria dos centros de endocrinologia pelo seu baixo custo, diferentemente do teste com CRH, e pela mais simples aplicabilidade técnica frente ao cateterismo bilateral sequencial do seio petroso inferior e diante da dificuldade clínica e laboratorial em se estabelecer o diagnóstico diferencial entre DC e SAE e entre DC e PC, este trabalho busca avaliar a acurácia do teste da desmopressina na dose de 10 µg endovenosa nessas situações, através da elaboração de duas revisões sitemáticas e meta-análises.

O emprego dessa estratégia se justifica pois tanto DC e SAE são doenças com baixa prevalência na população geral [5, 16] em que o limitado número de estudos clínicos sobre o tema apresenta heterogeneidade em relação aos diferentes *cut-offs* diagnósticos propostos no teste da desmopressina, bem como em relação às características clínicas e laboratoriais das populações analisadas em cada estudo, podendo gerar imprecisão diagnóstica se não corretamente avaliada. [73] Como principal limitação desse tipo de estudo, temos que a precisão diagnóstica do teste a ser avaliado pode não ser considerada pelo paciente incluído como o principal desfecho a ser analisado [73] (não foi possível avaliar a importância dada pelos pacientes em relação aos falsos positivos e negativos).

1.2 Revisão sistemática de estudos de acurácia

A elaboração de uma revisão sistemática e meta-análise inicia pela definição da questão a ser respondida pela pesquisa, que em revisões sitemáticas de acurácia ela segue o acrônimo PIRO, P= participantes, I= teste índice estudado, R= referência considerada e O= desfechos analisados.[73]

Visando afastar se tal questionamento sobre a acurácia do teste da desmopressina nesses quadros já fora respondido, [73] uma busca breve foi realizada na *Cochrane Library*,

*Pubmed (*por meio do *Clinical Queries), TripDatabas e Centre for Reviews and Dissimenation* e não tendo sido encontrada nenhuma revisão sistemática e/ou protocolo para esse teste terapêutico, registramos nossas revisões e meta-análises no banco internacional de registros de revisões sistemáticas: PROSPERO.

As estratégias de busca na literatura devem se guiar pela definição dos termos a serem utilizados, evitando-se restrição de idioma e de data; a fim de que a revisão seja reprodutível, o processo de busca deve ser relatado. Dado que pode ocorrer viés de publicação, estudos não publicados devem ser pesquisados.[73]

Em relação à avaliação da eligibilidade, a triagem dos artigos deve se dar, inicialmente, pela leitura do título e resumo de forma independente, por uma dupla de revisores, sendo os estudos potencialmente elegíveis para inclusão na revisão selecionados para leitura na íntegra e posteriormente, avaliados quanto à adequação ao PIRO proposto. [73] Em caso de discordância nesse processo de seleção, um terceiro revisor deve ser consultado ou os revisores devem entrar em consenso. [73]

Os estudos considerados para inclusão na revisão têm seus principais dados extraídos seguindo-se uma ficha clínica padronizada a fim de se evitar comparar um teste diagnóstico realizado sob distinta metodologia ou em populações apresentando importante diversidade. [73] Posteriormente a essa etapa, avalia-se a qualidade metodológica dos estudos incluídos em relação ao risco de viés e a variabilidade existente, que pode gerar limitações em relação à aplicabilidade, [73] por meio da ferramenta QUADAS-2 (*Quality Assessment of Diagnostic Accuracy Studies*).[74]

A qualidade da evidência para estimativa de efeito do teste diagnóstico dos desfechos que puderam ser plotados na meta-análise foi gerada de acordo com o *GRADE (Grading of Recommendations Assessment, Development, and Evaluation Working Group),*[75] que avalia a qualidade na totalidade da evidência de determinada tecnologia em saúde sobre um desfecho, em especial aqueles mais importantes para o paciente.[76] Os cinco quesitos analisados e estudados são: o risco de viés dos estudos incluídos, imprecisão, inconsistência, evidência indireta e viés de publicação. [76]

Com base nos dados extraídos é possível calcular a tabela de contingência 2x2 onde inserem-se os verdadeiros postivos e negativos, bem como falsos positivos e negativos em relação ao teste diagnóstico frente à doença considerada e o seu padrão de referência considerado, possibilitando-se, assim, calcular sensibilidade (S), especificidade (E), valor preditivo positivo (VPP) e negativo (RVN), razão de verossimilhança positiva (RVP) e negativa (RVN) e razão de chances diagnóstica (dOR). [73]

A meta-análise de estudos de acurácia leva em consideração que os pontos de corte propostos, bem como as diferenças populacionais e metodológicas existentes em cada estudo podem influenciar os resultados obtidos, sendo assim, desaconselhada a utilização do modelo meta-analítico do efeito-fixo (combinação univariada). [77] Este considera que a variabilidade intra e inter estudos se deve ao acaso e que o efeito do teste diagnóstico seria semelhante entre os estudos.[77] Já o efeito randômico considera que a heterogeneidade não se deve ao "acaso" e sim, das diferenças existentes entre os estudos, podendo assim influenciar a magnitude dos resultados obtidos na análise; [77] portanto, em estudos de meta-análise, recomenda-se a utilização do modelo do efeito fixo apenas quando não houver heterogeneidade entre estudos ou quando poucos estudos forem incluídos.[77]

A razão de verossimelhancia é muito útil quando se avalia um teste diagnóstico, já que avalia se o mesmo é capaz de aumentar ou diminuir a probabilidade de ter uma doença em comparação com a prevalência dessa doença (probabilidade pré-teste) na população estudada. [73] RVP > 10 e RVN < 0,1 classificam o teste como apresentando bom desempenho diagnóstico [79]; contudo, tal análise combinada é desencorajada em meta-análises de acurácia, [80] já que desconsidera correlações entre RVN e RVP. [81]

A dOR é uma combinação estatística da sensibilidade, especificidade e dos valores de razão de verossimilhança positiva e negativa que expressa a razão de chances de o teste ser positivo naqueles portadores da doença em relação àqueles não doentes, sendo utilizada para construção dos intervalos de confiança da curva sROC [80]; porém, dado que avalia o produto entre falsos positivos e negativos e não o somatório dos mesmos, apresenta baixa aplicabilidade como ferramenta meta-analítica.[73, 80]

Considerando-se que os estudos de acurácia diagnóstica podem apresentar variabilidade intra e inter estudos, mesmo quando considerado um mesmo valor de corte como diagnóstico, [73] a utilização da sensibilidade e especificidade combinadas pelo modelo do efeito fixo não é satisfatória para classificar o desempenho de um teste [82] e a utilização do teste de inconsistência de Higgins ou I^2 [83] como ferramenta para analisar a heterogeneidade apresenta limitações, já que sensibilidade e especificidade são medidas dependentes nesse cenário. [80]

Assim, quando o teste diagnóstico sofre influência do ponto de corte utilizado entre os estudos incluídos, deve-se construir uma curva ROC sumária (sROC), que é uma imagem gráfica dos valores de sensibilidade e especificidade obtidos para todos os valores diagnósticos possíveis considerados, plotando-se os VP no eixo das ordenadas e os FP no das abcissas e, por modelo regressão linear, determinar um ponto na curva reproduzida para cada

estudo incluído. [73, 80] Ainda, quando a curva sumária produzida apresenta um formato simétrico, conclui-se que o teste a ser avaliado não apresenta variabilidade de distribuição dos resultados entre doentes e não doentes e assim, a dOR é constante ao longo de toda curva.[80]

Contudo, através da distribuição dos estudos em relação à sROC, pode se apenas inferir sobre a variabilidade inter e intra-estudos e realizar análises exploratórias por subgrupos [73] e assim, seu resultado é influenciado pelo número de estudos em cada subgrupo. Dessas limitações, através de modelos hierárquicos estendidos em meta-análise, pode-se calcular uma região de predição no espaço ROC de um futuro estudo a ser realizado, tendo em vista a incerteza em relação aos pontos sumários adotados, e assim, pela distribuição dos estudos nessa região, determinar a heterogeneidade entre eles.[84] Os modelos hierárquicos existentes são o bivariado, e o de Rutter e Gatsonis sROC (HSROC) [85, 86]; ambos utlizam uma análise binomial para avaliar a variabilidade intra-estudos, porém, na análise inter-estudos, (heterogeneidade) aquele sumariza as estimativas de sensibilidade e especificidade como uma média do "operating point" entre os estudos, em que os valores sumários estimados de S e/ou E sofrem influência de covariáveis; enquanto este propõe que todos os estudos teriam uma ROC com formato semelhante, permitindo assim configurar uma ROC "média" entre os estudos, que é influenciada pela heterogeneidade das covariáveis sobre S e E e pela posição e formato da ROC (cut-offs e parêmetros de acurácia utilizados por cada estudo); assim, a análise da S não se reduziria quando se aumentasse a E. [80]

Apesar de todas essas considerações em relação aos modelos hierárquicos, quando se obtém um número pequeno de estudos a serem avaliados pelo efeito randômico, o uso de ambos os modelos gera imprecisão; nessas situações, investigar os parâmetros inicialmente pelo efeito fixo, e posteriormente, considerar os resultados encontrados pelo efeito randômico pode ser uma estratégia, bem como avaliar o efeito da exclusão/inclusão de alguns estudos na análise final.[80]

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CAPÍTULO 2: Revisão sistemática e meta-análise da acurácia do teste da desmopressina na distinção entre doença de Cushing e síndrome de pseudo-Cushing

Systematic Review and Meta-Analysis of Desmopressin Test Accuracy for Differentiating Cushing's Disease from Pseudo-Cushing's Syndrome

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ABSTRACT

Purpose: We evaluated the accuracy of the desmopressin (1-deamino-8D-arginine vasopressin) test to differentiate Cushing's disease (CD) from pseudo-Cushing's syndrome (PCS). **Methods:** We conducted a systematic review of diagnostic test accuracy (DTA) studies in which patients with CD or PCS underwent the desmopressin test. The LILACS, PubMed, EMBASE, and CENTRAL Cochrane databases were searched. Two reviewers independently assessed the studies for their eligibility and risk of bias and extracted data. The meta-analysis used bivariate and hierarchical summary receiver operating characteristic models. The quality of the evidence was generated according to the Grading of Recommendations Assessment, Development and Evaluation Working Group criteria. **Results:** The five included DTA studies comprised 203 individuals; most of them had mild hypercortisolism. With low-certainty evidence, the pooled sensitivity for CD diagnosis was 89% (95% confidence interval [CI], 81–94%) and the specificity was 93% (95% CI, 87–97%). The test accuracy obtained by the symmetric summary receiver-operator characteristic (ROC) curve was 0.96 (95%CI, 0.94–0.98). The univariate pooled subgroup analysis according to the adrenocorticotropic hormone (ACTH) cutoff (> 4pmol/liter plus a basal serum cortisol > 331 nmol/liter vs. > 6 pmol/liter) showed sensitivities and specificities of 93% (83–98%) vs. 85% (70–94%) and 94% (83–99%) vs. 94% (84–99%), respectively, with no statistical differences. **Conclusion:** For patients suspected of CD and mild hypercortisolism, the desmopressin test can be useful to differentiate CD from PCS. Due to the low quality of evidence, patients from both groups should receive follow-up examinations. PROSPERO registration number: CRD42018085634

Keywords: Cushing's syndrome, Cushing's disease, Pseudo-Cushing's syndrome, Desmopressin, Systematic Review

INTRODUCTION

Cushing syndrome (CS) is caused by prolonged exposure to elevated levels of endogenous or exogenous glucocorticoids [1] and is characterized by signs and symptoms resulting from excessive concentrations of circulating free glucocorticoids, the loss of the hypothalamic-pituitary-adrenal axis regulation, and inconsistency in the circadian rhythm of cortisol secretion [1].

The most frequent etiology of endogenous CS in adults is Cushing's disease (CD), which accounts for approximately 70% of CS cases [2]. This condition results from the increased production of adrenocorticotropic hormone (ACTH) due to a pituitary adenoma and has an incidence and prevalence of 2–3 cases per 1,000,000 inhabitants/year and 40 cases per 1,000,000 inhabitants, respectively [3].

Patients with hypercortisolism present higher morbidity and mortality than the general population [4-6], particularly due to complications such as systemic arterial hypertension, diabetes mellitus, dyslipidemia, and cardiovascular disease [7]. These patients are also more likely to develop infections due to immunosuppression [7].

Pseudo-Cushing's syndrome (PCS) (also named pseudo-Cushing's states) is a medical condition in which patients present with mild to moderate ACTH-dependent hypercortisolism. [1,8,9] PCS represents a heterogeneous group physiological (surgery-associated stress, severe illness, or emotional stress) or non-physiological (chronic alcoholism and withdrawal syndrome, major depression, polycystic ovary syndrome, obesity, or poorly controlled diabetes mellitus) disorders that lead to increased cortisol production as well as the clinical and laboratory features seen in CS [1,8-11]

Due to the increasing prevalence of individuals with one of the conditions that characterize PCS and the fact that many patients with endogenous hypercortisolism may not have the most specific signs and symptoms of this hormonal disorder (easy bruising, capillary fragility, proximal weakness, and reddish-purple striae), the need to differentiate these two clinical situations also occurs increasingly more frequently.

Distinguishing PCS from CS can be challenging [7]. Indeed, screening tests used to diagnose CS, such as the 24-h urinary free cortisol (UFC), late-night salivary cortisol and dexamethasone suppression tests may be inaccurate and unable to exclude a diagnosis of CS [8,12,13]. The most widely used tests to differentiate these two conditions have been the dexamethasone-suppressed corticotropin-releasing hormone (CRH) stimulation test (DEX-CRH test) [13-16] and, more recently, the desmopressin stimulation test [17]. In its original publication [18], the DEX-CRH test showed a 100% accuracy; however, this finding was not

reproduced in subsequent studies [14-16]. Furthermore, due to the high cost and unavailability of ovine CRH, its use is currently limited [12].The desmopressin test has the advantage of being inexpensive and of high diagnostic accuracy; however, different cutoff values have been proposed [17, 19-23].

Thus, we aimed to evaluate the diagnostic accuracy of the desmopressin test at a dose of 10 μg intravenously for differentiation between CD and PCS.

METHODOLOGY

A systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [24] and was reported according to the PRISMA-Diagnostic Test Accuracy Studies (DTAs) criteria [25]. The protocol was registered in the International Prospective Registry of Systematic Reviews (ID: CRD42018085634).

Eligibility criteria

We included DTA studies that followed the PIRO structure described below.

Population (P)

Patients with clinical suspicion of endogenous CS and with at least two different screening tests for hypercortisolism: 24-hour urinary free cortisol (UFC), salivary cortisol at 00:00, dexamethasone suppression test (DST 1 mg) or no cortisol suppression with 2 mg dexamethasone for 48h.

Test Index (I)

We considered as test index desmopressin at a dose of 10 μg intravenously, with serum cortisol and plasma ACTH collected at -15 and 0 minutes before the application of desmopressin and 15, 30, 45, 60, and 90 minutes after drug administration.

Reference Test (R)

Patients with an ACTH-secreting pituitary adenoma in pathologic analysis after pituitary surgery were considered to have CD [1,12,26-28]. Patients who did not undergo surgery were considered to have CD if their plasma ACTH was >20 pg/mL [12, 26-28] along with one of the following criteria: bilateral inferior petrosal sinus sampling with a central-to-peripheral ratio of plasma ACTH concentrations ≥ 2.0 pg/mL before or ≥ 3.0 pg/mL after the

administration of CRH or desmopressin [27-31]; a pituitary adenoma measuring > 6 mm on magnetic resonance imaging (MRI) in a patient with concordant results suggestive of CD in the high-dose dexamethasone suppression test and CRH stimulation test [12, 26, 27, 32,33].

We considered as being PCS one of the following disorders: major depression, obsessive-compulsive disorder, anxiety disorder, polycystic ovary syndrome (PCOS), chronic alcoholism, severe obesity [8-10, 15], and whose follow-up showed a hypercortisolism resolution after control of the disease associated with PCS [8-10, 15].

Outcomes (O)

The performance measure of the desmopressin test compared to the reference test was assessed via a 2×2 contingency table, in which true-positive, false-positive, false-negative, and true-negative cases were computed for the diagnosis of CD. From these data, the accuracy of the index test (sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio) was calculated.

Exclusion Criteria

We excluded studies with patients who received a CD diagnosis without presenting the confirmatory criteria described above, as well as studies with PCS whose patients did not receive outpatient follow-up for evaluation of hypercortisolism after resolution of the disease associated with PCS.

Search Strategies

Four general search strategies were created for the EMBASE (1980-10/01/2019), PubMed (1966-10/01/2019), LILACS (1982-10/01/2019), and CENTRAL (Cochrane Collaboration Controlled Trials Registry-10/01/2019) (supplemental data) electronic databases. The index terms Cushing's disease and desmopressin were used to construct each search strategy with no language or year restrictions.

Additionally, we searched for eligible studies in the Trip Medical Database, SCOPUS, Web of Science, and CINAHL. We also searched thesis banks and ClinicalTrials.gov for unpublished and ongoing studies, respectively.

We used EndNote software to download references, remove duplicates, and facilitate the selection process.

Study Selection

Two reviewers independently and in pairs (RRG and MVGC) selected titles and abstracts from the references identified by the bibliographic research. Potentially eligible studies were selected for full-text review and evaluated for conformance to the proposed PIRO. In case of disagreements during the selection process, we arrived at a consensus via discussion. The reasons for each excluded study were justified.

Data Extraction and Management

For each study, both reviewers extracted data on the study characteristics and the corresponding participant-related information. For each comparison between index and reference tests, data were extracted on the number of true positives, true negatives, false positives, and false negatives in the form of a two-by-two table.

Risk of Bias and Applicability

We evaluated the risk of bias corresponding to the included studies via the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [34].

Unit of Analysis

The unit of analysis was the aggregate data extracted from the journal publications

Assessment of Heterogeneity

Inconsistencies among the study results were ascertained by visually inspecting forest plots and by the results of Higgins or I^2 tests, in which $I^2 > 50\%$ indicated a moderate probability of heterogeneity [35].

Synthesis of Results (Meta-analysis)

A 2 X 2 contingency table was constructedfor each study. We calculated the sensitivity, specificity, and likelihood ratios (LRs). When the primary study had 0 in a cell of the 2 X 2 table, the value of 1 was added to perform the calculations [36]. This happened in two studies.

We performed the meta-analytical summaries using bivariate and hierarchical summary receiver operating characteristic (HSROC) models in Stata, MetaDiSC, and RevMan versions 12, 1.4, and 5.3, respectively.

Due to the small number of studies, a univariate model was used for sensitivity and

subgroup analyses.

Sensitivity Analyses

To assess the robustness of our results, we performed sensitivity analysis according to the threshold of the desmopressin test.

Grading the Quality of Evidence

For each outcome, a tabulated summary of the findings was produced to report the effectiveness of the index test and the certainty of the evidence was measured using the Grading of Recommendations Assessment, Development, and Evaluation Working Group (GRADE) approach [37].

RESULTS

Study Selection

The search strategies yielded 1,779 references. After removing duplicates, 1,696 studies remained (Fig. 1). Sixteen studies potentially eligible for inclusion in the review were selected for reading in full. However, of these, 11 were excluded: one was a narrative review article [1], seven did not use the desmopressin test as the index test [18,38-43], in one study the authors used the desmopressin test to differentiate CD from patients with clinical and laboratory suspicion of CS and, although most patients with suspicion of CS had at least one positive screening test for hypercortisolism, they were not classified as carriers of PCS [19]. Two studies compared the desmopressin test in CD versus patients with depression; however, the patients with depression did not present clinical or laboratory features of CS [44,45].

Study Characteristics

Per our eligibility criteria, we included five studies comprising 203 participants (97 with CD and 106 with PCS) [20,22,23,46,47].Three of the included studies also had a group of healthy individuals who underwent desmopressin tests[20,22,23]. Table 1 describes these studies.

The patients in the included studies were suspected of having endogenous CS and most had mild hypercortisolism. The definition of mild hypercortisolism was similar between studies. Tirabassi et al. defined mild hypercortisolism as 24-h UFC below < 771 nmol/day, while Moro et al. and Giraldi et al. defined it as UFC < 690 nmol/day. All studies performed

intravenous desmopressin tests by the slow bolus administration of 10 μg in the antecubital vein after nocturnal fasting, followed by measurement of plasma ACTH and serum cortisol levels at -15 minutes, 0, 10, 20, 30, 45, 60, 90, and 120 minutes (Coiro et al. did not measure these hormone levels at 120 minutes). The baseline ACTH and cortisol values were the means of the respective measurements between -15 and 0 minutes before desmopressin administration. The absolute peak of ACTH elevation was defined as the greatest value occurring between 0 and 30 minutes after medication. The absolute increase in plasma ACTH levels after the desmopressin test was defined as the difference between the values at 0 minutes and the highest value reached within 30 min (delta-ACTH).

Regarding the criteria to differentiate CD from PCS, two studies defined CD as delta-ACTH > 4 pmol/L along with a baseline serum cortisol threshold >331 nmol/L [22][23], while two studies defined CD as a delta-ACTH >6 pmol/L [20][46] and one study used an ACTH increase >2.2-fold (15 minutes vs. basal) and cortisol increase >1.5-fold (30 minutes vs. basal) to differentiate CD from PCS [47].

Risk of Bias and Applicability

The overall methodological quality of all the included studies is summarized in Figure 2. Of the five studies, only Giraldi et al. did not clearly state whether all PCS patients had two tests that confirmed hypercortisolism; therefore, the applicability to patients was unclear. Coiro et al.[47] did not describe the criteria used to characterize patients as having CD; therefore, the applicability and risk of bias regarding the reference test were also unclear. Tirabassi et al. 2011 [23] included some patients that had already been in Tirabassi et al. 2010 [22]; therefore, the patient selection was considered unclear. The risks of bias in the other domains were low.

Meta-analysis

The pooled sensitivity for distinguishing CD from PCS was 89% (95% CI, 81–94%, 203 participants, Fig. 3) and the specificity was 93% (95% CI, 87%-97%). The positive and negative likelihood ratio values were 13.6 (95% CI, 6.6 – 28) and 0.12 (95% CI, 0.067–21), respectively. The diagnostic odds ratio was 114.6 (95% CI, 41.8–314). The test accuracy according to symmetric summary receiver-operator characteristic (ROC) curve analysis was 0.96 (95% CI, 0.94–0.98: Fig. 4A).

The univariate pooled analysis according to ACTH cutoff (>4 pmol/liter and a basal serum cortisol >331 nmol/liter vs. > 6 pmol/liter) showed sensitivities and specificities of

93% (83–98%) vs. 85% (70–94%) and 94% (83–99%) vs. 94% (84–99%), respectively (Table 2). The indirect comparison did not show a statistical difference; the ratios for sensitivity and specificity were 1.09 (95% CI, 0.94-–.27, p=0.26) and 0.99 (95% CI, 0.9–1.1, p=0.92), respectively.

As some patients described in Tirabassi et al. 2011 [23]. were also included in Tirabassi et al. 2010 [22], we performed a summary analysis including only Tirabassi et al. 2010 [22], Giraldi 2007 [46], and Moro et al. 2000 [20]. The univariate pooled sensitivity was 0.86 (95% CI, 0.74–0.93) and the specificity was 0.94 (95% CI, 0.86–0.98). The AUC for the symmetric ROC curve was 88.04% (Table 2).

Our analyses did not show high levels of heterogeneity, with an I^2 of 0% (95% CI, 0–100%, Fig.3). In addition, the prediction region was similar to the confidence region (where heterogeneity is high; the 95% prediction region is much larger than the 95% confidence region) [48] (Fig.4B).

Quality of the evidence

The evidence was downgraded in two levels due to imprecision (small studies with < 100 participants), outcomes limited by the diagnostic accuracy, and lack of evaluation of other important aspects from the patient's point of view such as quality, stress, and costs caused by a false-positive diagnosis. Therefore, the quality of evidence was low according to the GRADE criteria. Investigation of publication bias was not possible due to the small number of included studies (<10) [48].

DISCUSSION

Considering the need to distinguish CD from PCS, we evaluated the accuracy of the desmopressin test to differentiate these two conditions. We then performed a systematic review of the literature and identified five studies that met our eligibility criteria [20,22,23,46,47]. The pooled sensitivity and specificity for CD showed that, with a CD prevalence of 48%, 43 and 48 of 100 patients with mild hypercortisolism will have CD and PCS, respectively, according to desmopressin test. Among individuals with CD, the desmopressin test will miss five patients (11% of 48); however, these patients can be tested again. Of the 52 patients without CD, four may be unnecessarily referred for MRI and, sometimes, for bilateral inferior petrosal sinus sampling and surgery.

The positive likelihood ratio expressed the probability of a positive result in people with a clinical condition when compared to that for a non-clinical condition [49]. The

combined value found in our meta-analysis was 13.6 (95% CI, 6.6–28); the value above 10 classifies the test as having good performance, with a positive result more likely to be "true positive" than "false positive"[49]. The likelihood ratio of a negative test measured how much more likely a negative test was to occur in disease than in non-disease [49]. The combined LR score was 0.12 (95% CI, 0.067–21); although it was not < 0.1 [49], the test presented good performance since the prevalence of CD in the population was rare; thus, a negative result was more likely to be a "true negative" than a "false negative" [24].

The sROC curve is one of the most reliable tools for the analysis of test accuracy [35,52], allowing calculation of the expected sensitivity over a range of values chosen for specificity. AUC values between 0.9–1.0 as in our study, indicate an "excellent" diagnostic accuracy [50]. The symmetrical shape of the curve indicates that the presence of CD with mild hypercortisolism did not result invariability in ACTH and cortisol value distributions during the test, with a constant dOR value throughout the curve [24].

To our knowledge, this is the first systematic review and meta-analysis to differentiate CD from PCS. In the literature, the Dexa-CRH test (a combined test with the administration of CRH after the 48-h, 2 mg/day low-dose dexamethasone suppression test) discriminated between CS and PCS [18, 51]. Yanovski was the first to use the Dexa-CRH for CS and proposed a serum cortisol value >1.4 μg/dL (absolute value) after 15 minutes as suggestive of CS, with an accuracy of 100% [18] .Erickson et al. [14] and Giraldi et al. [46] evaluated the Dexa-CRH test to differentiate CD from PCS; based on the above cortisol cutoff proposed by Yanovski [18], they achieved 100% sensitivity and specificities of 76% and 62.5%, respectively. Erickson et al. [14] reported 95% sensitivity and 97% specificity in ROC analysis of ACTH values greater than 27 pg/mL (5.9 pmol/L) at 15 minutes after CRH stimulus. Considering the controversies regarding the accuracy of the Dexa-CRH test, as well as the high cost and worldwide unavailability of CRH, the desmopressin test has been proposed to differentiate these clinical conditions.

The primary limitation of this review and meta-analysis was the number of studies included (five) and the number of patients included per study (<100) [48]. The second limitation was that our use of the hierarchical model in the meta-analysis required including a study which some patients had been included in previous studies also included in the present review [23]; moreover, one study did not use a threshold to differentiate DC from PCS [23]. Meanwhile, the sensitivity analysis in Table 2 showed that the univariate analysis including only the three other studies had results similar to those of the first analysis. It should also be noted that our results concern a subgroup of patients with CD and mild hypercortisolemia,

which may be a greater diagnostic challenge, since “first-line” tests for CS may be inconclusive.

CONCLUSION

Implications for practice

Based on the results of this systematic review and meta-analysis, we conclude that the desmopressin test shows good accuracy in differentiating patients with CD from those with PCS, especially individuals with mildly elevated UFC. The indirect comparisons did not show statistical differences between the two ACTH cut-offs used in the literature; namely, a delta-ACTH > 4 pmol/liter plus a basal serum cortisol > 331 nmol/liter and a delta-ACTH > 6 pmol/liter. However, due to the low quality of evidence in our results, individuals with PCS by desmopressin test should be followed up and retested in case of changes in their CS-related symptoms.

Implications for research

Future studies should include comparisons between different thresholds to CD disease from PCS states.

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CONFLICT OF INTERESTS

No conflict to declare.

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Table 1. Characteristics of the studies included in relation to the "PIRO" and to the contingency table

Study/ Country	Study Design	PC Descriptions	Assays	UFC 24 h Mean (SEM) CD/PC	Index Test Descriptions/Cut-off	Reference Test Description	Participants	TP DC/PC	FP DC/PC	TN DC/PC	FN DC/PC	Follow-up
Tirabassi, 2011 Italy	Retrospective comparative evalution in a consecutive cohort	PC: 18 MD (12), PCOS + panic disorder (8)	ACTH: I (Immulite; Diagnostic Products Corp., Los Angeles, CA) Cortisol and UFC: I (Advia Centaur; Bayer Diagnostics Newbury, UK)	DC: 859.4 nmol/24 h (562 -1692.6) PC: 533.8 nmol/24h (455.7-606.9)	DT 10 µg 30 CC, 18 PC, 12 CG Basal cortisol >331 nmol/L and Delta ACTH > 4 pmol /L	DC:pituitary surgery and/or postoperative clinical and biochemical resolution of hypercortisolism	30 CD 18 PC 12 CG	29	0	18	1	-
Tirabassi, 2010 Italy*	Retrospective comparative evalution in a consecutive cohort	PC:16 MD, 2 oh, 9 PCOS, 1 panic disorder + nervous bulimia	ACTH: I (Immulite; Diagnostic Products Corp., Los Angeles, CA) Cortisol and UFC: I (Advia Centaur; Bayer Diagnostics Newbury, UK)	DC: 778 nmol/24h (484.2 - 1,545) PC: 526.9 nmol/24h (461.3 to 620.7)	DT 10 ug 52 CD (23 mildly), 28 PC, 31 CG Basal cortisol >331 nmol/L and ACTH > 4 pmol /L	DC:pituitary surgery and/or postoperative clinical and biochemical resolution of hypercortisolism	52 DC 28 PC 31 CG	20*	2	26	3*	3 years
Giraldi, 2007* Italy	Retrospective comparative evalution in a consecutive cohort	PC: truncal obesity (17) and/or PCOS (8) and/or MD (10) and/or OH (2)	ACTH: IRMA (Allegro, Nichols Institute Diagnostics, San Juan Capistrano, CA) Cortisol: RIA (Byk-Sangtec Diagnostica, Dietzenbach, Germany or DPC Immulite, Los Angeles, CA, USA) UFC: RIA (DPC, Los Angeles, CA, USA)	DC: 707·7 nmol/24h (+/- 87.0) PC: 279.7 nmol/24h (+/-41.15)	DT 10 µg 27 CD (19 mildly), 21 PC Delta ACTH > 6 pmol/L	DC:pathology on transsphenoidal surgery specimen	29 CD 23 PC 32 SC	15*	2	19	4*	3,1 years for PC

Moro, 2000* Italy	Retrospective comparative evalution in a consecutive cohort	30 PC	ACTH: IRMA (Allegro, Nichols Institute Diagnostics, San Juan Capistrano, CA) Cortisol: RIA (Byk-Sangtec Diagnostica, Dietzenbach, Germany) UFC: RIA (DPC, Los Angeles, CA)	DC: 818 nmol/24h (+/- 122.14) PC: 321.7 nmol/24h (+/- 27.81)	DT 10 µg 76 CD (20 mildly), 30 PC Delta ACTH > 6 pmol/L	DC:pituitary surgery and/or postoperative clinical and biochemical resolution of hypercortisolism	76 CD 30 PC 36 obesity 31 CG	18*	1	29	2*	2 years for PC
Coiro, 2000 Italy	Retrospective comparative evalution in a consecutive cohort	PC: 8 (OH)	RIA Laboratorial kits not cited	DC: 220 µg/24h (+/- 18.2) PC: 199.4 µg/24h (+/- 9.5)	DT 10 µg 6 CD, 8 PC CD: ACTH increase > 2.2 times (t 15´ vs. basal) and cortisol increase > 1,5 times (t 30´vs. basal)	Radiological findings of pituitary ?	6 DC 8 PC 9 CG	6	0	8	0	-

CA: California; CS: Cushing syndrome; CD: Cushing disease; CG: control group; DST: supression test with dexamethasone; DT: desmopressin test; FP: false positive; FN: false negative; I: immunometric; IRMA: immunoradiommetric; iv: intravenous; MD: major depression; PC: pseudo-Cushing; PCOS: polycystic ovarian syndrome; RIA: radioimmunoassay; SEM: standard error of mean; TP: true positive; TN: true negative; UFC: urinary free cortisol; UK: United Kingdom; USA: United States of America *: patients with CD and mildly elevated UFC 24 h. – no information provided

Table 2. Summaring of the proposed "PIRO" and the univariated analysis

What is the diagnostic accuracy of desmopressin test to differentiate Cushing disease from pseudo Cushing?					
Population: Patients suspected for Cushing syndrome presenting laboratorial mild hypercortisolism					
Prior testing: None					
Settings: Ambulatory health care settings					
Index test: Desmopressin at a dose of 10 µg intravenously, with serum cortisol and plasma ACTH dosages					
Reference standard: Adrenocorticotropic producing hormone in the pathologic analysis after pituitary surgery					
Importance:Accurate and fast diagnosis allows appropriate and quick treatment for Cushing disease and no need of additional exams for pseudo Cushing					
Studies: Consecutive series of patients, five studies, presenting 203 individuals					
Quality concerns: few studies and sparse data					
Test/subgroup	**Summary accuracy (95 % CI)**	**Number of Participants**	**Prevalence**	**Implications**	**Quality Comments**
Cut-off delta ACTH > 6 pmol/liter	Sensibility 85% (70%-94%) Specificity 94% (84%-99%)	90 (2 studies) &	40/90= 44%	With a CD prevalence of 44%, 37 out of 100 patients with mild hypercortisolism will have CD by DT and six will be missed (15% of 44), but can be tested again. Of the 56 patients without CD, three may be unnecessarily referred for MRI, and sometimes for PSC and surgery	Low numbers of patients per study (<100). No clear information regarding the criteria used to characterize patients as having CD. Withdrawals no reported.
Cut-off delta ACTH > 4 pmol/liter plus a cortisol > 331 nmol/L	sensitivity 93% (83%-98%) specificity 94% (83%-99%) sensitivity 87% (66%-	51 (1 study) *	23/51=45%	With a CD prevalence of 45%, 39 out of 100 patients with mild hypercortisolism will have CD by DT and six will be missed (13% of 45), but can be tested again. Of the 55 patients without CD, four may be unnecessarily referred for MRI, and sometimes for PSC and surgery	Low numbers of patients per study (<100). No clear information regarding the criteria used to characterize patients as having CD. Withdrawals no reported.

	97%)* specificity 93% (76%-99%)*				
ACTH 2.2 and cortisol 1.5 times higher than baseline	sensitivity 86% (42%-100%) specificity 94% (52%-100%)	14 (1 study)#	6/14: 43%	With a CD prevalence of 43%, 37 out of 100 patients with mild hypercortisolism will have CD by DT and six will be missed (14% of 43), but can be tested again. Of the 57 patients without CD, three may be unnecessarily referred for MRI, and sometimes for PSC and surgery	Low numbers of patients per study (<100). No clear information regarding the criteria used to characterize patients as having CD. Withdrawals no reported
Tirabassi 2010, Giraldi 2007 and Moro 2010	sensitivity 86% (74% - 93%) specificity 94% (86% - 98%)	141 (3 studies)	62/141=44%	With a CD prevalence of 44%, 38 out of 100 patients with mild hypercortisolism will have CD by DT and six will be missed by the DT (14% of 44), but can be tested again. Of the 56 patients without CD, three may be unnecessarily referred for MRI, and sometimes for PSC and surgery	Low numbers of patients per study (<100). No clear information regarding the criteria used to characterize patients as having CD. Withdrawals no reported.

CD: Cushing disease; DT: desmopressin test; * including only Tirabassi 2010, PSC: Petrous Sinus Catheterization; #: including only Coiro 2000; &: including Moro 2000 and Giraldi 2007.

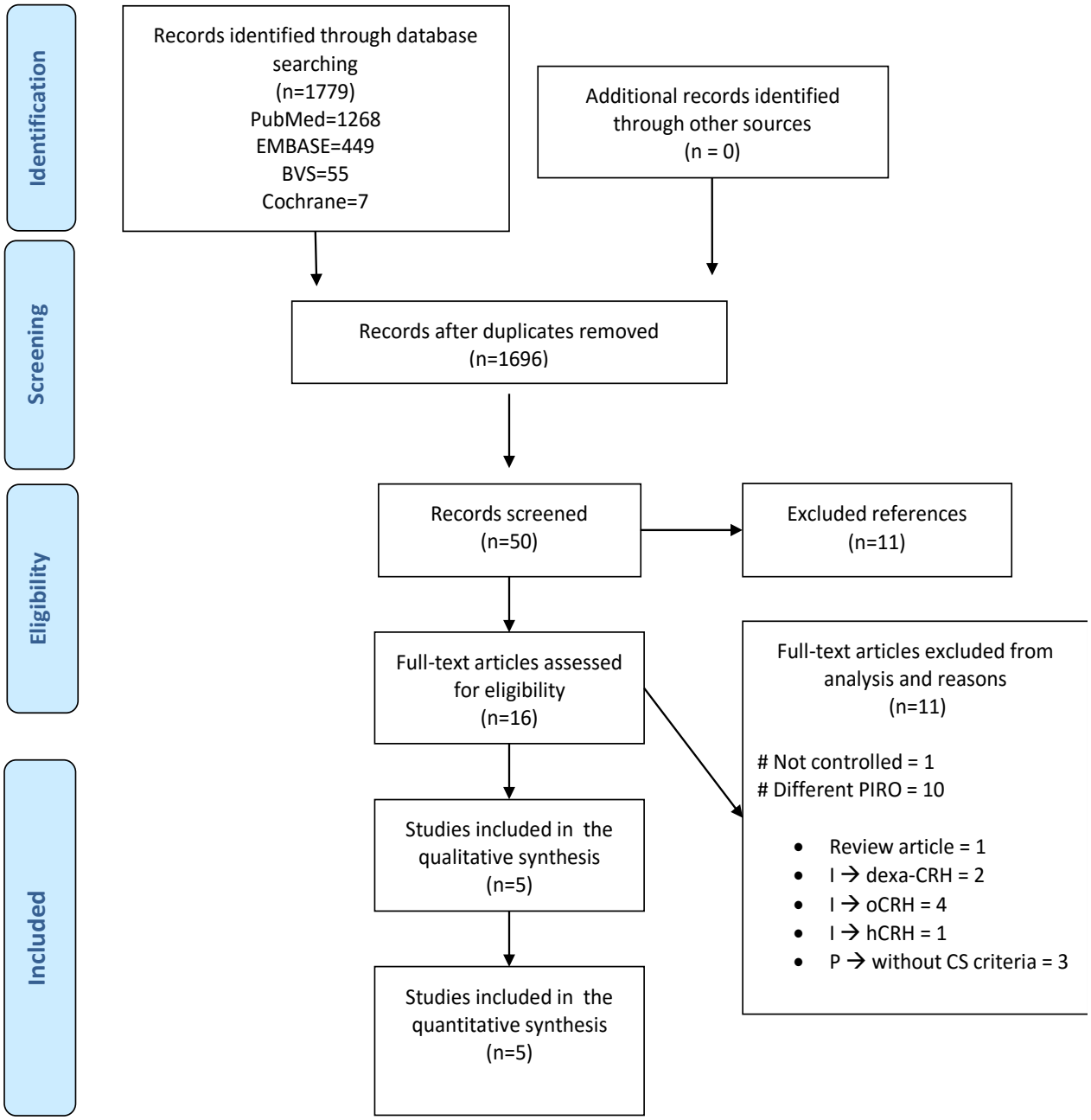

Figure 1. Flowchart for identifying eligible studies. BVS=Biblioteca Virtual da Saúde; CRH=corticotropin releasing hormone; CS=Cushing´s syndrome; dexa-CRH=dexamethasone-suppressed CRH test; hCRH=human CRH; I=index test; oCRH=ovine CRH; O=outcomes; P=patients; R=reference test.

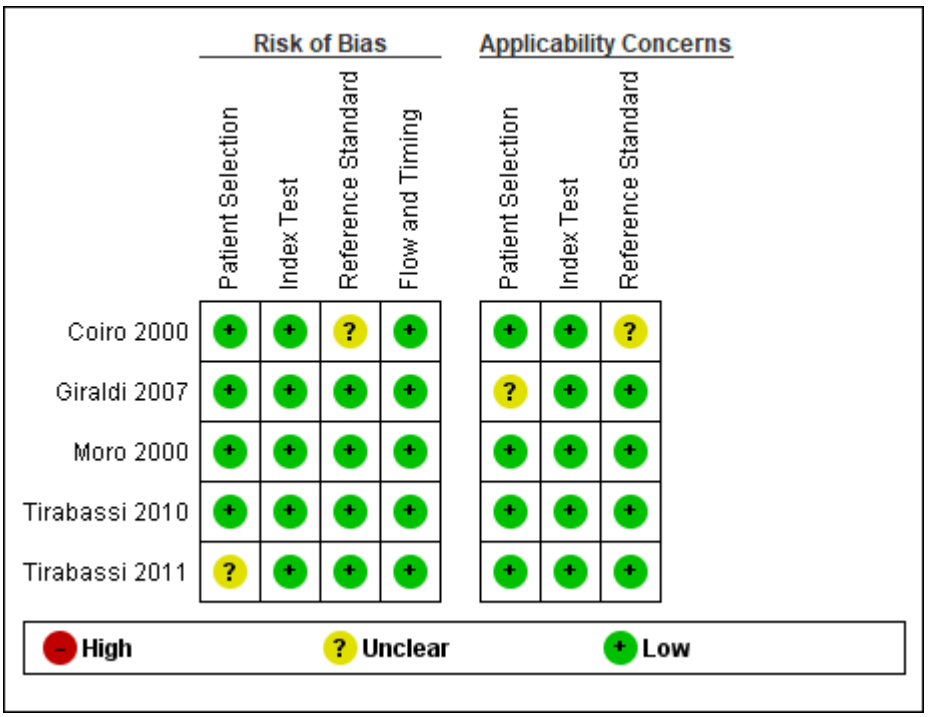

Figure 2. Risk of bias and applicability: authors' judgment on each domain for each included study

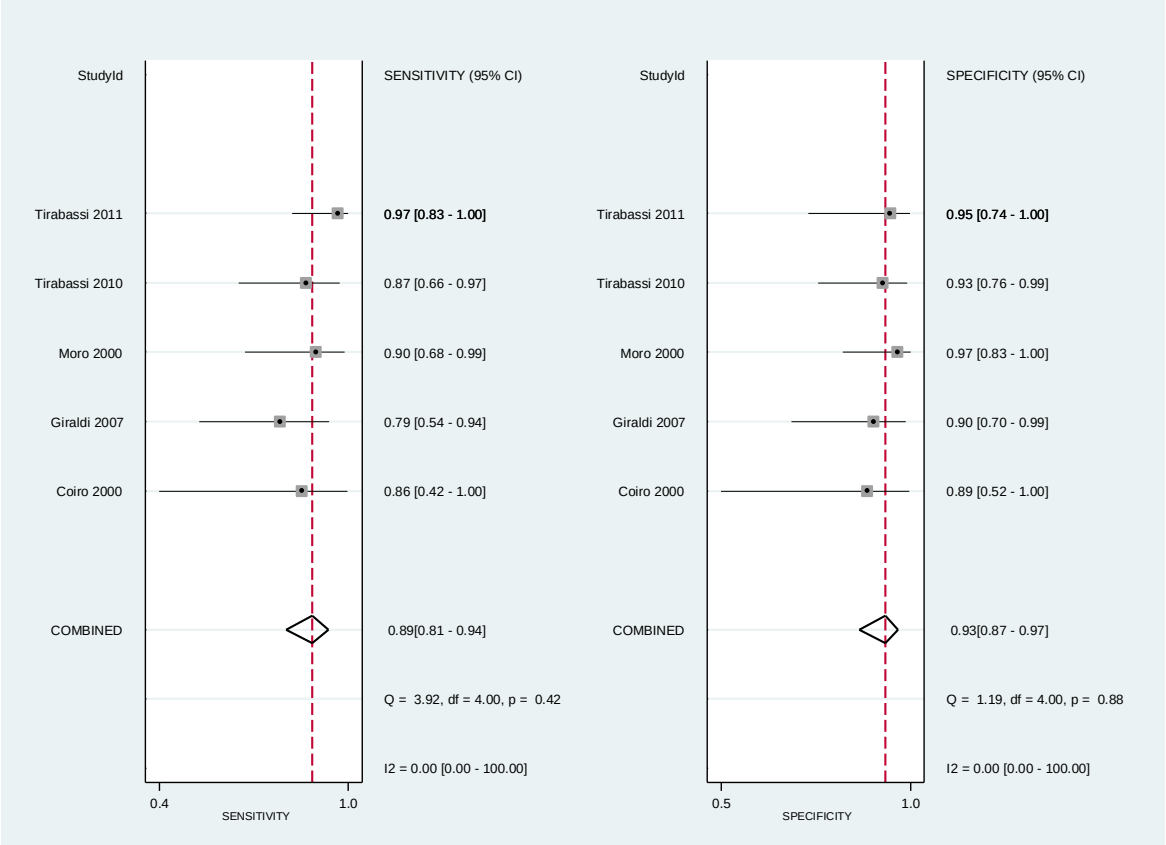

Figure 3. Forest plot for individual studies and pooled sensitivity and specificity for desmopressin test accuracy. Q: chi-squared statistic; df: degrees of freedom;I^2: inconsistency of studies' results. Dashed line means the mean number found across studies.

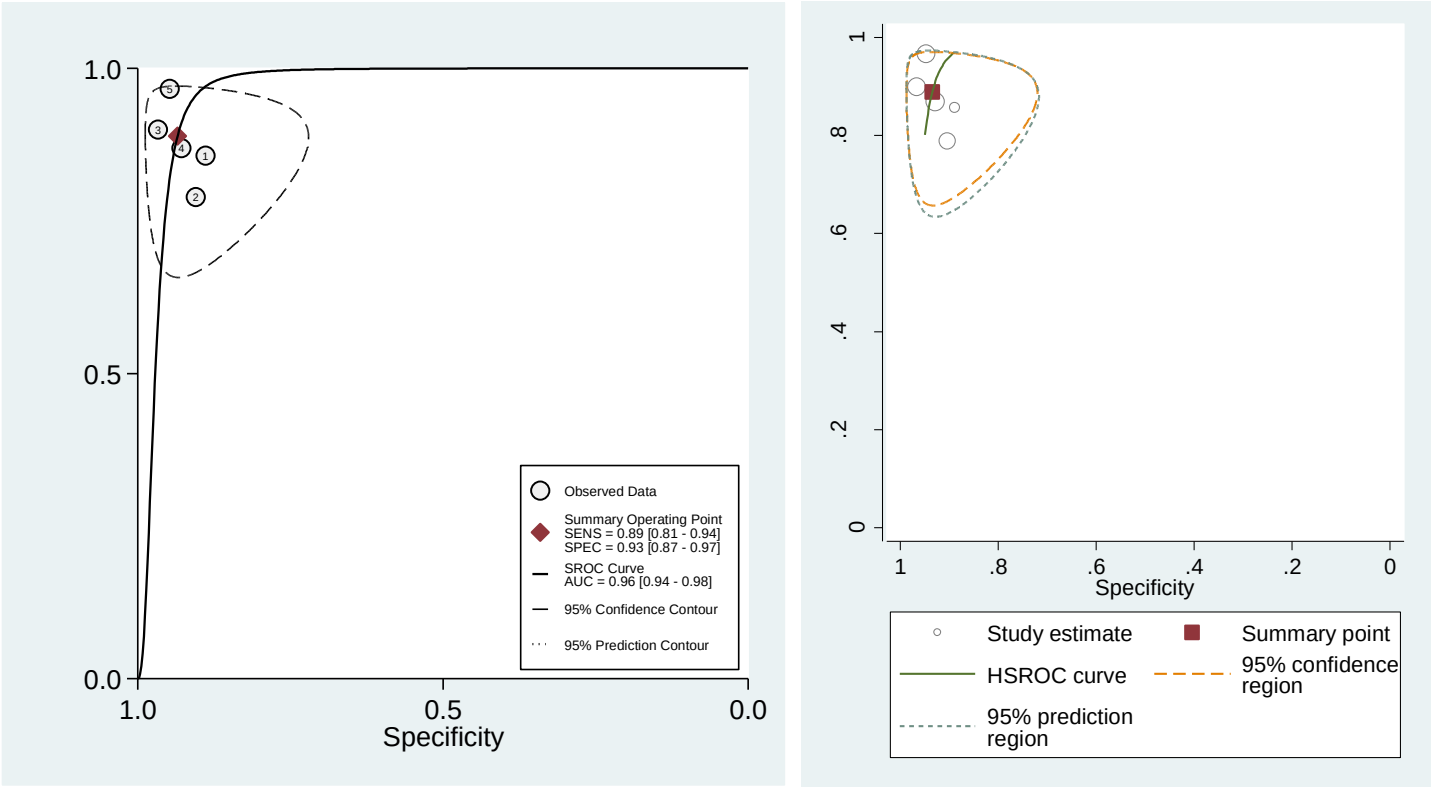

Figure 4. A. ROC curve for desmopressin test accuracy, five studies included**. B.** Hierarchical summary receiver-operator curve (HSROC) of the five studies plotted in the meta-analysis, the confidence region represents uncertainty in the overall average value caused by sampling variability, the prediction region represents variation from between study heterogeneity.

APPENDIX

Appendix 1 - Research Strategy

PUBMED – 01/10/2019

#1 "**Pituitary ACTH Hypersecretion"[Mesh]** OR (ACTH Hypersecretion, Pituitary) OR (Hypersecretion, Pituitary ACTH) OR (Cushing Disease, Pituitary) OR (Cushing Diseases, Pituitary) OR (Pituitary Cushing Disease) OR (Pituitary Cushing Diseases) OR (Pituitary-Dependant Hypercortisolism Disorder) OR (Hypercortisolism Disorder, Pituitary-Dependant) OR (Hypercortisolism Disorders, Pituitary-Dependant) OR (Pituitary Dependant Hypercortisolism Disorder) OR (Pituitary-Dependant Hypercortisolism Disorders) OR (Pituitary-Dependant Cushing Syndrome) OR (Cushing Syndrome, Pituitary-Dependant) OR (Pituitary Dependant Cushing Syndrome) OR (Pituitary-Dependant Hypercortisolism) OR (Hypercortisolism, Pituitary-Dependant) OR (Hypercortisolisms, Pituitary-Dependant) OR (Pituitary Dependant Hypercortisolism) OR (Pituitary-Dependant Hypercortisolisms) OR (Cushing Disease) OR (Disease, Cushing) OR (Pituitary Cushing Syndrome) OR (Cushing Syndrome, Pituitary) OR (Inappropriate ACTH Secretion Syndrome) OR (Inappropriate Adrenocorticotropic Hormone Secretion) OR (Adrenocorticotropic Hormone, Inappropriate Secretion) OR "**Cushing Syndrome"[Mesh]** OR (Syndrome, Cushing) OR (Cushing's Syndrome) OR (Syndrome, Cushing's) OR (Hypercortisolism) OR ACTH Secreting Pituitary Adenoma OR "**ACTH-Secreting Pituitary Adenoma"[Mesh]** OR (ACTH-Secreting Pituitary Adenomas) OR (Pituitary Adenomas, ACTH-Secreting) OR (Corticotroph Adenoma) OR (Adenoma, Corticotroph) OR (Adenomas, Corticotroph) OR (Corticotroph Adenomas) OR (Pituitary Corticotropin-Secreting Adenoma) OR (Corticotropin-Secreting Adenoma, Pituitary) OR (Corticotropin-Secreting Adenomas, Pituitary) OR (Pituitary Corticotropin Secreting Adenoma) OR (Pituitary Corticotropin-Secreting Adenomas) OR (ACTH-Producing Pituitary Adenoma) OR (ACTH Producing Pituitary Adenoma) OR (ACTH-Producing Pituitary Adenomas) OR (Pituitary Adenoma, ACTH-Producing) OR (Pituitary Adenomas, ACTH-Producing) OR (Pituitary Adenoma, ACTH-Secreting) OR (Pituitary Adenoma, ACTH Secreting)

#2 **"Deamino Arginine Vasopressin"[Mesh]** OR (Vasopressin, Deamino Arginine) OR

(Arginine Vasopressin, Deamino) OR (Desmopressin) OR (1-Deamino-8-D-arginine Vasopressin) OR (Vasopressin, 1-Deamino-8-D-arginine) OR (1-Desamino-8-arginine Vasopressin) OR (Vasopressin, 1-Desamino-8-arginine) OR (Adiuretin SD) OR (Apo-Desmopressin) OR (Apotex Brand of Deamino Arginine Vasopressin) OR (DDAVP) OR (Desmospray) OR (Octostim) OR (Ferring Brand 1 of Desmopressin Acetate) OR (Octim) OR (Desmopressine Ferring) OR (Ferring, Desmopressine) OR (Desmotabs) OR (Nocutil) OR (Norgine Brand of Desmopressin Acetate) OR (Hoyer Brand of Desmopressin Acetate) OR (Desmopressin Acetate) OR (Acetate, Desmopressin) OR (Desmopressin Monoacetate, Trihydrate) OR (Monoacetate, Trihydrate Desmopressin) OR (Trihydrate Desmopressin Monoacetate) OR (Desmopressin Monoacetate) OR (Monoacetate, Desmopressin) OR (IQFA Brand of Desmopressin Acetate) OR (Minirin) OR (Minurin) OR (Ferring Brand 2 of Desmopressin Acetate) OR (Adiuretin) OR (Desmogalen) OR (Galen Brand of Desmopressin Acetate) OR (Ddavp test*) OR **"Corticotropin-Releasing Hormone"[Mesh]** OR (Corticotropin Releasing Hormone) OR (ACTH-Releasing Hormone) OR (ACTH Releasing Hormone) OR (Corticoliberin) OR (CRF-41) OR (Corticotropin-Releasing Factor-41) OR (Corticotropin Releasing Factor 41) OR (Corticotropin-Releasing Hormone-41) OR (Corticotropin Releasing Hormone 41) OR (CRF (ACTH)) OR (ACTH-Releasing Factor) OR (ACTH Releasing Factor) OR (Corticotropin-Releasing Factor) OR (Corticotropin Releasing Factor)

Total: 1268

EMBASE – 01/10/2019

'Cushing disease'/exp OR ‘adrenocortical hyperplasia, acth induced’ OR ‘corticotropin induced adrenocortical hyperplasia’ OR ‘Cushing disease’ OR ‘cushing syndrome, acth induced’ OR ‘Cushings disease’ OR ‘itsenko cushing disease’ OR ‘pituitary ACTH hypersecretion’ OR **'ACTH secreting adenoma'**/exp OR ‘ACTH-secreting pituitary adenoma’ OR ‘ACTH producing adenoma’ OR ‘ACTH producing adenomas’ OR ‘ACTH producing pituitary adenoma’ OR ‘ACTH producing pituitary adenomas’ OR ‘ACTH producing pituitary tumor’ OR ‘ACTH producing pituitary tumors’ OR ‘ACTH producing pituitary tumour’ OR ‘ACTH producing pituitary tumours’ OR ‘ACTH producing tumor’ OR ‘ACTH producing tumors’ OR ‘ACTH producing tumour’ OR ‘ACTH producing tumours’ OR ‘ACTH secreting adenomas’ OR ‘ACTH secreting pituitary adenoma’ OR ‘ACTH

secreting pituitary adenomas’ OR ‘ACTH secreting pituitary tumor’ OR ‘ACTH secreting pituitary tumors’ OR ‘ACTH secreting pituitary tumour’ OR ‘ACTH secreting pituitary tumours’ OR ‘ACTH secreting tumor’ OR ‘ACTH secreting tumors’ OR ‘ACTH secreting tumour’ OR ‘ACTH secreting tumours’ OR ‘adrenocorticotropic hormone secreting adenoma’ OR ‘corticotroph adenoma’ OR ‘corticotroph adenomas’ OR ‘corticotropinoma’ OR ‘corticotropinomas’

'desmopressin'/exp OR ‘(1 deamino 8 dextro arginine) vasopressin’ OR ‘1 deamine 8 d arginine vasopressin’ OR ‘1 deamino 8 d arginine vasopressin’ OR ‘1 deamino 8 dextro arginine vasopressin’ OR ‘1 desamino 8 d arginine vasopressin’ OR ‘8 (1 desaminoarginine) vasopressin’ OR ‘[1 deamino 8 d arginine] vasopressin’ OR ‘[1 deamino 8 dextro arginine] vasopressin’ OR ‘[deamino 8 cysteine d arginine] vasopressin’ OR ‘[deamino 8 cysteine dextro arginine] vasopressin’ OR ‘[deamino 8 dextro arginine] vasopressin’ OR ‘adin’ OR ‘adiuretin’ OR ‘adiuretin sd’ OR ‘adiuretin-sd’ OR ‘concentraid’ OR ‘d-void’ OR ‘dav ritter’ OR ‘DDAVP’ OR ’DDAVP (needs no refrigeration)’ OR ‘DDAVP desmopressin’ OR ‘DDAVP melt’ OR ‘DDAVP nasal’ OR ‘DDAVP rhinal tube’ OR ‘DDAVP tablets’ OR ‘deamino 8 dextro arginine vasopressin’ OR ‘deamino 8d arginine vasopressin’ OR ‘deamino dextro arginine vasopressin’ OR ‘deaminovasopressin [8 d arginine]’ OR ‘defirin' OR 'defirin melt’ OR ‘desmirin’ OR ‘desmomelt’ OR ‘desmopresina’ OR ‘desmopressin acetate’ OR 'desmopressin acetate (needs no refrigeration)’ OR ‘desmopressin acetate preservative free’ OR ‘desmopressin diacetate’ OR ‘desmopressin nasal solution’ OR ‘desmopressina’ OR ‘desmopressine’ OR ‘desmospray' OR ‘desmotab’ OR ‘desmotabs’ OR ‘desmotabs melt’ OR ‘desurin’ OR ‘emosint’ OR ‘enupresol’ OR ‘minirin’ OR ‘minirin DDAVP’ OR ‘minirin melt’ OR ‘minirin nasal spray’ OR ‘minirin rhinetten’ OR ‘minirin rhinyle’ OR ‘minirin spray’ OR ‘minirinette’ OR ‘minirinmelt’ OR ‘minrin’ OR ‘minurin’ OR ‘minurin flas’ OR ‘minurin gotas’ OR ‘miram’ OR ‘nictur’ OR ‘noctisson’ OR ‘nocturin’ OR ‘nocutil’ OR ‘nordurine’ OR ‘novidin’ OR ‘nucotil nasenspray’ OR ‘octim’ OR ‘octostim’ OR ‘octostim nasal spray’ OR ‘octostim spray’ OR ‘presinex’ OR ‘stimate’ OR ‘vasopressin 8 (1 desaminoarginine)’ OR ‘vasopressin’ OR ‘1 deamino 8 dextro arginine’ OR ‘vasopressin’ OR ‘deamino 8 dextro arginine’ OR ‘vasopressin [1 (3 mercaptopropionic acid) 8 dextro arginine]’ OR ‘vasopressin [1 deamino 8 dextro arginine]’ OR ‘vasopressin [deamino 8 cysteine dextro arginine]’ OR ‘vasopressin [deamino 8 d arginine]’ OR ‘vasopressin [deamino 8 dextro arginine]’ OR ‘vasopressin [deamino dextro arginine]' OR 'wetirin’

Total: 449

LILACS / IBECS/ MEDCARIB / BBO / BDENF (BVS – IAHX) – 01/10/2019

- Descriptor in portuguese: Hipersecreção Hipofisária de ACTH
- Synonyms in portuguese:
- Hipersecreção de ACTH Hipofisária
- Hipersecreção de ACTH Pituitária
- Hipersecreção Pituitária de ACTH
- Doença de Cushing
- Síndrome da Secreção Inadequada de ACTH
- Secreção Inadequada de Hormônio Adrenocorticotrópico
- C10.228.140.617.738.250.725
- C19.700.355.800
- Descriptor in portuguese: Síndrome de Cushing
- C19.053.800.367
- Descriptor in portuguese: Desamino Arginina Vasopressina
- Synonyms in portuguese:
- Desmopressina
- Desaminoarginina Vasopressina
- D06.472.699.631.692.781.100.250
- D12.644.400.900.100.250
- D12.644.456.925.100.250
- D12.644.548.691.692.781.100.250
- D12.776.641.650.937.100.250
- Search strategy
- #1 MH:"Hipersecreção Hipofisária de ACTH" OR (Hipersecreção de ACTH Hipofisária) OR
- (Hipersecreção de ACTH Pituitária) OR (Hipersecreção Pituitária de ACTH) OR (Doença de Cushing) OR
- (Síndrome da Secreção Inadequada de ACTH) OR (Secreção Inadequada de Hormônio Adrenocorticotrópico)
- OR MH:C10.228.140.617.738.250.725$ OR MH:C19.700.355.800$
- #2 MH:"Síndrome de Cushing" OR
- MH:C19.053.800.367$

- #3 MH:"Desamino Arginina Vasopressina" OR (Desmopressina) OR (Desaminoarginina Vasopressina)
- OR MH: D06.472.699.631.692.781.100.250$ OR MH: D12.644.400.900.100.250$ OR MH: D12.644.456.925.100.250$
- OR MH: D12.644.548.691.692.781.100.250$ OR MH: D12.776.641.650.937.100.250$

Total: 55

CENTRAL - COCHRANE – 01/10/2019

ID	Search Hits	
#1	MeSH descriptor: [Pituitary ACTH Hypersecretion] explode all trees	18
#2	MeSH descriptor: [Cushing Syndrome] explode all trees	88
#3	MeSH descriptor: [Deamino Arginine Vasopressin] explode all trees	345
#4	Cushing disease	312
#5	#1 or #2 or #4	352
#6	#3 and #5	7

Total: 7

CAPÍTULO 3: Revisão sistemática e meta-análise da acurácia do teste da desmopressina na distinção entre doença de Cushing e síndrome do ACTH ectópico.

Systematic Review and Meta-Analysis of the Desmopressin Test Accuracy in the differentiation of the Cushing´s disease from the ectopic ACTH syndrome

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ABSTRACT

Purpose: We evaluated the accuracy of 10 µg desmopressin test to differentiate Cushing's disease (CD) from ectopic ACTH syndrome (EAS). **Methods**: We conducted a systematic review of diagnostic test accuracy (DTA) studies in which patients with DC or EAS were submitted to the desmopressin test. Four search strategies were created from LILACS, PubMed, EMBASE, Cochrane Central Register of Controlled Trials. Two reviewers independently assessed the studies for their eligibility, risk of bias and data extraction. Hierarchical and bivariate models on Stata software were used for meta-analytical summaries. **Results**: Eight studies were included, and to distinguish CD from EAS after desmopressin test, seven studies (331 participants) used an ACTH percent increment (Δ%), and seven (175 participants) used a cortisol Δ%. The pooled sensitivity for CD diagnosis was 0.83 (95% Confidence Interval (CI), 0.78-0.87) for ACTH Δ% and 0.80 (95% CI, 0.72-0.85) for cortisol Δ%. In both the analyses the 95% prediction intervals (PI) were not near the CI and for individuals with CD, 17% (15%-28%) will be missed by the desmopressin test. However, for specificity in regard Δ% ACTH and cortisol, the analyses showed high levels of heterogeneity between studies, which can be seen from both the hierarchical summary ROC curve plot (PI far from CI) and the Stata output (0.62 (CI, 0.45-0.77) and 0.68 (CI, 0.48-0.83), respectively. Only one study evaluated the sensitivity and specificity of a composite rule requiring an ACTH increase and a cortisol increase, whose values were 0.65 (CI,0.38-0.86) and 0.75 (CI, 0.19 – 0.99), respectively. **Conclusion**: The specificity of desmopressin test to distinguish CD from EAS has been very heterogeneous. Although the uncertainty in the sensibility is much lower, our results suggest that an average of 20% of CD diagnosis would be lost by this test. PROSPERO registration number: CRD42017068317

Keywords: Cushing's Disease, Desmopressin, ectopic ACTH syndrome

INTRODUCTION

Cushing's disease (CD) is the main etiology of endogenous Cushing's syndrome (CS), accounting for about 70% of the causes [1], with an incidence of 2-3 cases/1000,000 inhabitants year and prevalence of 40 cases / 1000,000 inhabitants [2], having high morbidity and mortality [3–5] and higher prevalence in females (3-8:1), [2,6] being the microadenomas the most frequent pituitary tumors responsible for the disease. [7–9]

The principal differential diagnosis of CD is CS secondary to ectopic production of ACTH (EAS), which correspond to between 10 and 20% of the causes of ACTH-dependent SC, and between 5-10% of SC. [10,11] It has been closely associated with small cell lung carcinoma (SCLC) [11], as well as pulmonary, thymic, pancreatic neuroendocrine tumors (NETs), pheochromocytoma, and medullary thyroid carcinoma [10–12]; however, in up to 20% of cases the ACTH source may remain hidden. [10,12,13] Unlike CD, EAS affects older [14,15], having a female-male distribution of 0.6-1:1 [10,16], and may present more aggressive clinical picture depending on the tumor in question [10,12], being difficult, just for the clinical evaluation, its distinction of the CD. [10,12] Altered tumor expression of the pro-opiomelanocortin gene product (POMC) is one of the best known involved in EAS [17] and although patients with EAS secondary to SCLC usually have plasma ACTH and serum cortisol values higher than CD, many patients with EAS and CD present overlap in these tests, [7,10,12] and therefore, they cannot be used to distinguish between CS ACTH dependent.

As pituitary microadenomas account for approximately 80-90% of cases of CD [7–9] and may correspond to pituitary incidentalomas present in up to 10% of the population, [18] the latest consensus [19,20] have recommended that in the differentiation of dependent CS ACTH, the presence of a pituitary lesion larger than or equal to 6 mm in pituitary magnetic resonance imaging may be considered when associated with high-dose dexamethasone suppression (HDDST) or suppression after CRH test [21–23]. It is also noteworthy that HDDST has low diagnostic accuracy between CD and EAS [10,12,24–26] and that the human and ovine CRH test [27–29] have high cost and unavailability in Brazil and worldwide. [20]

The gold standard to differentiate CD from EAS is the bilateral and simultaneous catheterization of the inferior petrous sinus (BSCIPS), which presents a diagnostic accuracy of 90-98% [30–32]. However, in addition to being invasive, the BSCIPS is limited in worldwide due to the need for highly qualified professionals to do so [20] and may have serious complications. [33,34] Aiming to overcome such diagnostic difficulties and considering the positive results found by Malerbi [35] with the intravenous desmopressin test

in the distinction between CD and EAS, our objective was to evaluate the diagnostic accuracy of the 10 μg desmopressin test in the distinction between CD and EAS.

METHODOLOGY

A systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [36] and was reported on according to the PRISMA - Diagnostic Test Accuracy Studies (DTAs) Statements. [37] Its protocol was registered in the International Prospective Registry of Systematic Reviews, under the ID, CRD42017068317

Eligibility criteria

We included DTA studies that followed the "PIRO" structure described below.

Patients (P)

Patients with ACTH-dependent CS were included.

Index test (I)

Desmopressin at a dose of 10 μg intravenously, with serum cortisol and plasma ACTH collected at the time -15 and 0 minutes prior to the application of desmopressin, and later at times 15, 30, 45, 60, 90, 120 minutes after the drug administration

Reference test (R)

Patients with an ACTH secreting pituitary adenoma in the pathologic analyses after pituitary surgery were considered as having CD [20,22,25,32,38] or if the hypercortisolism improved after surgery. For patients not undergoing surgery, we considered as having CD in the presence of a plasma ACTH > 20 pg/mL, [20, 22, 32, 38] and one of the following criteria: bilateral inferior petrous sinus sampling with a central-to-peripheral ratio of plasma ACTH concentrations ≥ 2.0 before or ≥ 3.0 after the administration of CRH or desmopressin [32, 38–41]; a pituitary adenoma > 6 mm on magnetic resonance imaging (MRI) [20] with concordant results suggestive of CD in the high-dose dexamethasone suppression test and CRH test. [22, 42–44]

The diagnosis of the EAS was performed by immunohistochemical analysis of tumor tissue; in the absence of surgery or if immunohistochemistry was negative for ACTH expression, which can occur in up to 30% of EAS [12, 45, 46], we considered bilateral

inferior petrous sinus sampling catheterization [47] or hypercortisolism improvement after surgery.

Outcomes (O)

The performance measure of the desmopressin test compared to the reference test was assessed by the 2x2 contingency table in which the true positive, false positive, false negative and true negative cases were computed for the diagnosis of CD. From these data, the accuracy of the index test (sensitivity, specificity, positive and negative likelihood ratio) was calculated.

Exclusion criteria

Patients who received the diagnosis of CD or EAS without presenting the criteria described above as confirmatory to the condition were not included.

Search strategy

Four general and adaptive search strategies were created for the electronic databases: EMBASE (1980-10/01/2019), PubMed (1966-10/01/2019), LILACS (1982-10/01/2019), and CENTRAL (Cochrane Collaboration Controlled Trials Registry 01/10/2018) (supplemental data). The mesh terms: Cushing's disease and desmopressin were used to construct each search strategy; there were no language or year restrictions.

Additionally, we surveyed the Trip Medical Database, SCOPUS, Web of Science, and CINAHL. Furthermore, we searched thesis banks for unpublished studies and ClinicalTrials.gov for ongoing studies.

We used the Endnote software to download references, remove duplicates, and facilitate the selection process.

Selection of Studies

Two reviewers independently (RRG and EGP) selected titles and abstracts from the ones identified via the bibliographic research. Potentially eligible studies were selected for a full reading and, subsequently, evaluated for conformance to the proposed PIRO. In case of disagreements during the selection process, we arrived at a consensus via discussions. The reasons behind each excluded study were justified.

Data extraction and management

For each study, both reviewers extracted data on the characteristics of the study and the corresponding participant-related information. For each comparison of index test with reference test, data were extracted on the number of true positives true negatives, false positives and false negatives in the form of a two by two table.

Risk of bias and applicability

We evaluated the risk of bias corresponding to the included studies via the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool. [48]

Unit of Analysis

The unit of analysis was the aggregate data extracted from the journal publications

Synthesis of Results (Meta-analysis)

For each study, a 2x2 contingency table was constructed. We calculated sensitivity, specificity and likelihood ratios. When the primary study had 0 in a cell of the 2x2 table, the value of 1 was added, so calculations could be done [49]; this happened in two studies.

We performed meta-analyses using a hierarchical and bivariate models, which accounts for intra-study accuracy variability and inter-study variations in test performance with inclusion of random effects. [36]

Given results from investigations of heterogeneity, we used the bivariate model to estimate summary sensitivity and specificity (summary points) and hierarchical summary receiver operating characteristic (ROC) model to estimate summary ROC curves.

For analyses, we used Stata Statistical Software V.16 (StataCorp LLC) and Review Manager 5 (RevMan 5) Software V. 5.3.

Assessment of Heterogeneity

Heterogeneity has been assessed visually using the plots in forest and ROC spaces. Variability away from the summary ROC curve is likely to represent greater heterogeneity then variation along the summary ROC curve, which might just correspond to simple threshold effects. If the number of studies included was appropriated, we would assess the following possible sources of heterogeneity: patient characteristics, test methods, study design. A separate sROC curve would be fitted for each subgroup, and the results could be compared graphically across subgroups. [36]

Sensitivity Analyses

If the number of studies was enough, we would assess the robustness of our results performing sensitivity analysis according to threshold of ACTH and cortisol percent increment after desmopressin test.

Grading the Quality of Evidence

For each outcome, a tabulated summary of the findings was produced to report the effectiveness of the index test and the certainty of the evidence was measured using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation Working Group) [50]

RESULTS

Study Selection

The search strategies yielded 1,779 references, and after removing the duplicates, 1,696 studies remained. After analyzing the titles and abstracts, fourteen studies that could fulfill the inclusion criteria defined were selected for complete reading (Figure 1) [24, 35, 44, 51–61]. However, of these, six were excluded for the following reasons: one study [54] included patients previously included in a published series [44], Testa et al., [60] did not present patients with EAS in their series; Colombo et al. did not confirm the EAS diagnosis [60]; Salgado et al., [24] evaluated the desmopressin test in patients with EAS and there were no patients with CD in their series; Sakai [53] and Suda [52] performed desmopressin test with 5 µg and 4 µg of desmopressin, respectively.

Study

Per our eligibility criteria, we included eight studies, 526 participants, 396 with ACTH dependent syndrome, 345 of them submitted to desmopressin test (291 with CD and 54 with EAS [35, 44, 51, 55–58, 61]. Two of the studies included also had a group of healthy individuals who were submitted to desmopressin test [35, 61]; table 1 presents the descriptive data of the studies.

All included studies used 10 µg of intravenous desmopressin and measured plasma ACTH and serum cortisol at -15 minutes, 0, 15, 30, 45, 60, 90 and 120 minutes (only Terzolo [61] excluded the 120 minute time in his protocol).

Regarding the criteria to distinguish CD from EAS from desmopressin test, eight

studies calculated sensibilities and specificities for separate values of ACTH and cortisol percent increments [35, 44, 51, 55–58, 61]. Barbot study [51] evaluated the accuracy only by ACTH increment, and Malerbi [35] by cortisol. Price et al. [55] was the unique study which evaluated the sensitivity and specificity of a composite rule requiring both an ACTH and cortisol increase.

In Barbot study [51] , CD was suggested in the presence of an ACTH percentage > 32.3 % above the baseline value; Marova, > 30 % [56]; Vilar [44] and Terzolo [61] studies evaluated two ACTH percent increment values (> 35 and > 50%); Tsagarakis [57, 58] evaluated > 50% and Price [55] >35%. Terzolo also considered an ACTH percent increment value > 50 % or > 35 % plus a delta ACTH > 4.5 pmol/L.

Related to cortisol percent increment after desmopressin test, Price[55], Tsagarakis [57, 58] and Vilar [44] evaluated an increment value > 20 %; Vilar also evaluated > 50 % from baseline; Malerbi [35] evaluated an increment > 40 %; Marova > 30 % [56]; Terzolo considered a cortisol percent increment value > 20 % plus a delta cortisol > 193 nmol/L [61]. More details about the criteria used in each study to distinguish CD from ectopic ACTH syndrome are presented in table 2, as well as the data with respect to the proposed “PIRO”.

Risk of Bias and Applicability

The overall methodological quality of all included studies is summarized in figure 2. Two studies did not inform if patients were enrolled in a consecutive or random sample and were evaluated as having unclear risk of bias and unclear applicability concern for patient selection. [57, 58] Barbot et al. [51] did not pre specified the threshold use, then, we evaluated as being unclear applicability concern for the index test. For the other studies and domains, we evaluated as being low the risk of bias and applicability concern.

Meta-analysis

Considering an ACTH percent increment (Δ%) after desmopressin test, the overall sensitivity for CD diagnosis was 0.83 (95% Confidence Interval (CI), 0.78-0.87) and overall specificity was 0.62 (95% CI, 0.45-0.77): seven studies, 331 patients (three studies considered Δ% > 35%, two Δ% > 50%, one Δ% > 32.3%, one Δ% > 30%). [44, 51, 55–58, 61] Summary positive and negative likelihood ratios were 2.2 (95% CI 1.42 - 3.41) and 0.27 (95% CI 0.19-0.4), respectively.

As two studies in addition to a Δ% ACTH > 35% also evaluated a Δ% ACTH > 50%, [44, 61] we performed the meta-analysis with one study considering Δ% > 35%, [55] four Δ%

> 50%, one Δ% > 32.3% [51] and one Δ% > 30% [56] ; the overall sensitivity and specificity were not statistic different from the previous analyses: 0.85 (95% CI, 0.80-0.89) and 0.60 (95% CI, 0.48-0.73), respectively.

Regarding cortisol percent increment, the overall sensitivity was 0.80 (95% CI, 0.72-0.85) and the specificity was 0.68 (95% CI, 0.48-0.83): seven studies, 175 participants. [35, 44, 55–58, 61] Four studies considered a cortisol increase > 20%, one > 40%, [35] one > 30% [56], one considered a cortisol > 20% plus a delta cortisol > 193nmol/L. [61] Summary positive and negative likelihood ratio were 2.5 (95% CI, 1.40-4.41) and 0.30 (95% CI, 0.19-0.46), respectively.

Only one study [55] evaluated the sensitivity and specificity of a composite rule requiring an ACTH increase > 35% and a cortisol > 20%, whose values were 0.65 (95% CI,0.38-0.86) and 0.75 (95% CI, 0.19 – 0.99), respectively.

Investigations of heterogeneity

To visualize total variability in sensitivity and specificity, we present the data in forest and ROC scatter plots (Figure 3 and Figure 4 for a Δ% ACTH; Figure 5 and Figure 6 for Δ% cortisol). For Δ% ACTH, sensitivity of the seven studies ranged from 71% to 92%, and specificity from 25% to 90%; for Δ% cortisol the sensitivities ranged from to 73 to 92%, and specificities 40% to 91%. In both analyses, forest and ROC plots show greater variability in estimated specificity than sensibility across studies. In the graphical outputs from fitting the hierarchical model, the 95% confidence interval for the summary point of both Δ% ACTH and Δ% cortisol are very wide, and the prediction interval is wider than confident interval; it means that if new studies be included, the overall estimated will be far from the currently effect.

Sensitivity analysis

Due to small number of studies included, we could not assess the robustness of our results performing sensitivity analyses according to threshold of ACTH and cortisol percent increment.

Quality of evidence

The evidence was downgraded in two levels due to risk of bias regarding patient´s applicability and because the outcomes analyzed were limited to the diagnostic accuracy and other important aspects from the patient's point of view were not evaluated as: due quality,

stress and costs caused by a false positive diagnosis. Them, the quality of evidence according to the GRADE was low. Investigation of publication bias was not possible due to small number of studies included (< 10). [50]

DISCUSSION

Considering the need to distinguish CD from EAS, we evaluated the accuracy of desmopressin test to differentiate these two diagnoses. Then, we performed a systematic review of the literature, and found eight studies that met our eligibility criteria. The overall sensitivity and specificity for CD showed that, when we consider an increase of ACTH percent increment after desmopressin test, with a prevalence of 84 % of CD (278/331) among patients with ACTH dependent syndrome, 14 of CD individuals will be missed by the desmopressin test (17 % of 84). Of the 16 patients with EAS, 6 will be falsely considered as having CD (38 % of 16). The individuals with EAS falsely diagnosed as CD will be probably submitted to a magnetic resonance imaging and in absence of an adenoma higher than 0.6 mm, a BSCIPS will be performed, and the diagnose will be probably corrected. Conversely, the patients with CD but falsely diagnosed with EAS would be submitted to an extensive investigation in order to find out the ectopic ACTH production.

The interpretation of sROC curve is one of the most reliable tools to analyze the accuracy of a test, [62, 63] allowing to calculate the expected sensitivity over a range of values chosen for specificity. As CD is more prevalent than EAS, the need for finding actually positive cases is of overriding importance and a test with high/moderate accuracy should operate higher on the ROC curve, accepting a higher false positive in order to keep true positive high and false negative low.

This is the first systematic review with meta-analysis published in the literature to differentiate CD from EAS using desmopressin test. Vassiliadi and Tasagarakis [64] performed a narrative literature review in 2018 studying the role of desmopressin test in the diagnosis and follow up of CS and described all the studies we included in this study, except Vilar et al., [44] and concluded that the available data do not support a role of desmopressin in the differential diagnosis between these two conditions; however no data analyses were performed.

Desmopressin (1-deamino-S-D-arginine vasopressin) [20] is the synthetic analog of AVP with high selectivity for renal AVPR2 (V2) receptors, where it promotes a non-pressure anti-diuretic effect [65, 66]; with less affinity, in AVPR1B receptors (V3 or V1b), it produces an increase in ACTH secretion and potentiation of CRH actions in individuals with CD,

differently from healthy ones, [67, 68] possibly due to overexpression of the V3 receptor or the presence of an ectopic V2 receptor in the ACTH-producing pituitary tumor cells. [58, 68, 69] Tsagarakis et. al., [58] demonstrated that the elevations in ACTH and cortisol when performing the desmopressin test were possibly due to the presence of tumor V2R receptors in those with SAE, thus justifying the false positive results found in this review and meta-analysis.

Besides desmopressin test, other dynamic tests have been commonly used to differentiate CD from EAS [20]. Based on the fact that corticotropic pituitary tumors are sensitive to stimulation of corticotropin-releasing hormone (CRH) and may maintain suppression by glucocorticoids, while ectopic secretory tumors of ACTH usually not, [67, 70, 71] CRH test have been used with this [28, 29]; however, given its cost and unavailability in Brazil and worldwide, its use has been decreasing [20]. High-dose dexamethasone (HDDST) cortisol suppression has been also performed to differentiate these two diagnoses, [43, 44] and despite its low cost and good availability, it has low diagnostic accuracy [22, 26].

Regarding the limitations of this review and meta-analysis, the most important is related to the number of studies included (eight studies), and the number of patients included per study; except for Barbot study, the other studies included less than 100 patients per study. Due the low number of studies included (< 10), the presence of publication bias could not be evaluated.

CONCLUSION

Implications for practice

The specificity of desmopressin test to distinguish CD from EAS has been very heterogeneous. Although the uncertainty in the sensibility is much lower, our results suggest that an average of 20% of CD diagnosis would be lost by this test.

Implications for research

In the unavailability of BSCIPS to differentiate CD from EAS, future studies with new tests and/or combined tests and including different thresholds should be performed.

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Conflict of interests

No conflict to declare.

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Table 1. Characteristics of the studies included in relation to the "PIRO" and to the contingency table

Study/ Country	Study design	Patients	Patients descriptions	Assays	Reference test description	Index Test — Cut-off descriptions	TP CD/EAS	FP CD/EAS	TN CD/EAS	FN CD/EAS
Malerbi, 1993 Brazil	Retrospective evaluation	16 CD 1 EAS 10 adrenal CS 4 indeterminated 15 CG Desmopressin 10 µg: 13 CD + 1 EAS	CD: 2 patients ACTH < 20 pg/mL EAS: ACTH < 20 pg/mL	Cortisol: RIA (Baxter Travenol Diagnostics Inc., USA) ACTH:RIA/IRMA (Diagnostic Products Corporation, USA / CIS Bio International, France)	CD: biochemical remission, histology or IPSS	I: desmopressin 10 µg CD: cortisol increment >40-44%	12	0	1	1
Newell Price, 1997 England	Retrospective comparative evaluation in a consecutive cohort	17 DC 5 EAS 3 adrenal CS Only 4 EAS have ACTH and cortisol incremente evaluated	CD: 8 patients ACTH < 20 pg/mL EAS: ACTH ≥ 20 pg/ml	Cortisol: RIA (in-house unextracted nonchromatographic) ACTH: RIA (in-house Vycor Societe-A.T.A., Geneva, Switzerland, glass-extracted)	Histologically (24) IPSS (1 CD)	I: desmopressin 10 µg CD: ACTH increment >35% OR Cortisol increment >20%	12 14	3 1	1 3	5 3
Tsagarakis, 1999 Greece	Retrospective evaluation	20 obesity 25 CD 3 EAS 5 adrenal CS	EAS: ACTH > 20 pg/mL	Cortisol: RIA (Coat-A-Count, Cortisol RIA, Diagnostic Products Corporation, Los Angeles, CA, USA) ACTH: IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).	CD: 15 histology, 5 biochemical remission 5 IPSS EAS: IPSS	I: desmopressin 10 µg CD: ACTH increment >50% OR cortisol increment >20%	23 21	0 0	3 3	2 4

Terzolo, 2001 Italy	Retrospective comparative evaluation in a consecutive cohort	34 CD 9 EAS 30 CG Desmopressin: 19 CD, 5 EAS, 30 CG	CD: 2 patients ACTH < 20 pg/mL EAS: ACTH > 20 pg/mL	Cortisol: RIA (Sorin Biomedica, Saluggia, Italy) ACTH: IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).	CD: 29 histology, 5 AI after surgery EAS:8 after surgery; 1 occult (IPSS)	I: desmopressin 10 µg CD: ACTH increment > 35% + D > 4,5 pmol/L OR ACTH increment > 50% + D > 4,5 pmol/L OR ACTH increment > 35% OR ACTH increment >50% OR Cortisol increment > 20 % + D > 193 nmol/L	16.9 16 17 16 14.6	2 2 3 3 3	3 3 2 2 2	2.1 3 2 3 4.4
Tsagarakis, 2002 Greece	Retrospective evalution	26 CD 5 EAS	CD: 1 patient with ACTH < 20 pg/mL EAS: ACTH > 20 pg/mL	Cortisol: RIA (Coat-A-Count, Cortisol RIA, Diagnostic Products Corporation, Los Angeles, CA, USA) ACTH: IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA,	CD: 14 histology, 6 biochemical remission 6 IPSS EAS: after surgery (histology + IHQ)	I: desmopressin 10 µg CD: ACTH increment>50% OR cortisol increment>20%	21 19	3 3	2 2	5 7

USA).

Marova, 2008 Russia	Retrospective comparative evalution in a consecutive cohort	21 CD 11 EAS 11 CS adrenal 11 CG	CD and EAS: ACTH > 20 pg/mL	Cortisol: ICMA (Vitros ECI automatic analyzer (UK) ACTH: IRMA (CIS-bio International, France)	CD and EAS: histology and immunochemicall y	I: desmopressin 10 µg CD: ACTH increment>30% OR cortisol increment>30%	16 16	5 5	10 10	1 1
Vilar, 2008 Brazil	Retrospective comparative evalution in a consecutive cohort	46 CD 7 EAS 21adrenal CS Desmopressin: 21 CD, 4 EAS	DC: some patients with ACTH < 20 pg/mL EAS: ACTH > 20pg/mL	Cortisol: ICMA (Diagnostic Products Corporation, Immulite 2000, Los Angeles, CA) ACTH: IRMA/ICMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA / Diagnostic Products Corporation, Immulite 2000, Los Angeles, CA)	CD: ACTH immunostaining in the pituitary adenoma and/or reversal of hypercortisolism after surgery EAS: ACTH immunoreactivity of the neoplastic tissue (7) or IPSS	I: desmopressin 10 µg CD: ACTH increment ≥35% OR ≥50% OR Cortisol increment ≥20% OR ≥50%	18 16 16 10	1 0 1 1	3 4 3 3	3 5 5 11
Barbot, 2016 Italy	Retrospective comparative evaluation in a consecutive cohort	149 CD 21 EAS	CD: some patients with baseline ACTH <20pg/mL EAS: ACTH	Cortisol: RIA/ECLIA (Diagnostic Products Corp., Los Angeles, CA, USA/Beckman Coulter, Brea, CA, USA)	CD: biochemical remission after TSS, histology and/or temporary hypoadrenalism. EAS:histologicall	I: desmopressin 10 µg CD: ACTH increment > 32.3%	124	8	13	25

	>20 pg/mL	y (20); IPSS (1)
	ACTH: IRMA/ECLIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA / Roche Diagnostics, Indianapolis, IN, USA).	

AI: adrenal insufficiency; CA: California; CS: Cushing syndrome: EAS: ectopic ACTH syndrome; CD: Cushing disease; CG: control group; D: delta; ECLIA: automated electrochemiluminescent method; ICMA: immunochemiluminometric assay; IRMA: immunoradiommetric; IPSS: inferior petrosal sinus sampling; IHQ: immunohistochemistry; USA: United States of America

Table 2. Summaring of the proposed "PIRO" and the pooled sensitivities and specificities results

What is the diagnostic accuracy of desmopressin test to differentiate Cushing disease from ectopic ACTH syndrome?					
Population: Patients with ACTH-dependent CS					
Prior testing: None					
Settings: Ambulatory health care settings					
Index test: Desmopressin at a dose of 10 µg intravenously, with serum cortisol and plasma ACTH dosages					
Reference standard: Adrenocorticotropic producing hormone in the pathologic analysis or IPSS					
Importance: Accurate and fast diagnosis allows appropriate and quick treatment for Cushing disease and no need of additional exams for ectopic ACTH syndrome					
Studies: Consecutive series of patients, eight studies, presenting 526 individuals (345 submitted to the test)					
Quality concerns: few studies and sparse data					
Test/subgroup	Summary accuracy (95 % CI)	Number of Participants	Prevalence	Implications	Quality Comments
Cut-off: ACTH increment > 35% (3 studies); > 50% (2 studies); > 32.3% (1 study); > 30% (1 study)	Sensitivity 83% (78-87%) specificity 62% (45%-77%)	331 (7 studies)	278/331=84%	With a CD prevalence of 84%, 70 out of 100 patients with ACTH dependent Cushing syndrome will have CD in the test and 14 will be missed by the DT (17% 84). Patients with CD but falsely diagnosed with EAS would be submitted to an extensive investigation in order to find out the ectopic ACTH production. Of the 16 patients without CD, six may be unnecessarily referred for MRI, and sometimes for IPSS	Low numbers of patients per study (<100)- except Barbot. CD. Withdrawals no reported.
Cut-off:	sensitivity 82%	331	278/331=84%	With a CD prevalence of 84%, 69 out of 100 patients with	Low numbers of patients per study

ACTH increment > 35 % (1 study), > 50% (4 studies); > 32.3% (1 study); > 30% (1 study)	(77%-86%) specificity 63% (46%-78%)	(7 studies)		ACTH dependent Cushing syndrome will have CD in the test and 15 will be missed by the DT (18% 84). Patients with CD but falsely diagnosed with EAS would be submitted to an extensive investigation in order to find out the ectopic ACTH production. Of the 16 patients without CD, six may be unnecessarily referred for MRI, and sometimes for IPSS	(<100) – except Barbot CD. Withdrawals no reported.
Cut-off: Cortisol increment > 20 % (4 studies); > 40% (1 study); > 30% (1 study); > 20 % plus delta cortisol > 193 nmol/L (1 study)	sensitivity 80% (72%-85%) specificity 68% (48%-83%)	175 (7 studies)	142/175=81%	With a CD prevalence of 81%, 65 out of 100 patients with ACTH dependent Cushing syndrome will have CD in the test and 16 will be missed by the DT (20% 88). Patients with CD but falsely diagnosed with EAS would be submitted to an extensive investigation in order to find out the ectopic ACTH production. Of the 19 patients without CD, six may be unnecessarily referred for MRI, and sometimes for IPSS	Low numbers of patients per study (<100) Withdrawals no reported

CS: Cushing syndrome; DT: desmopressin test; EAS: ectopic ACTH syndrome; CD: Cushing disease; CG: control group; IPSS: inferior petrosal sinus sampling

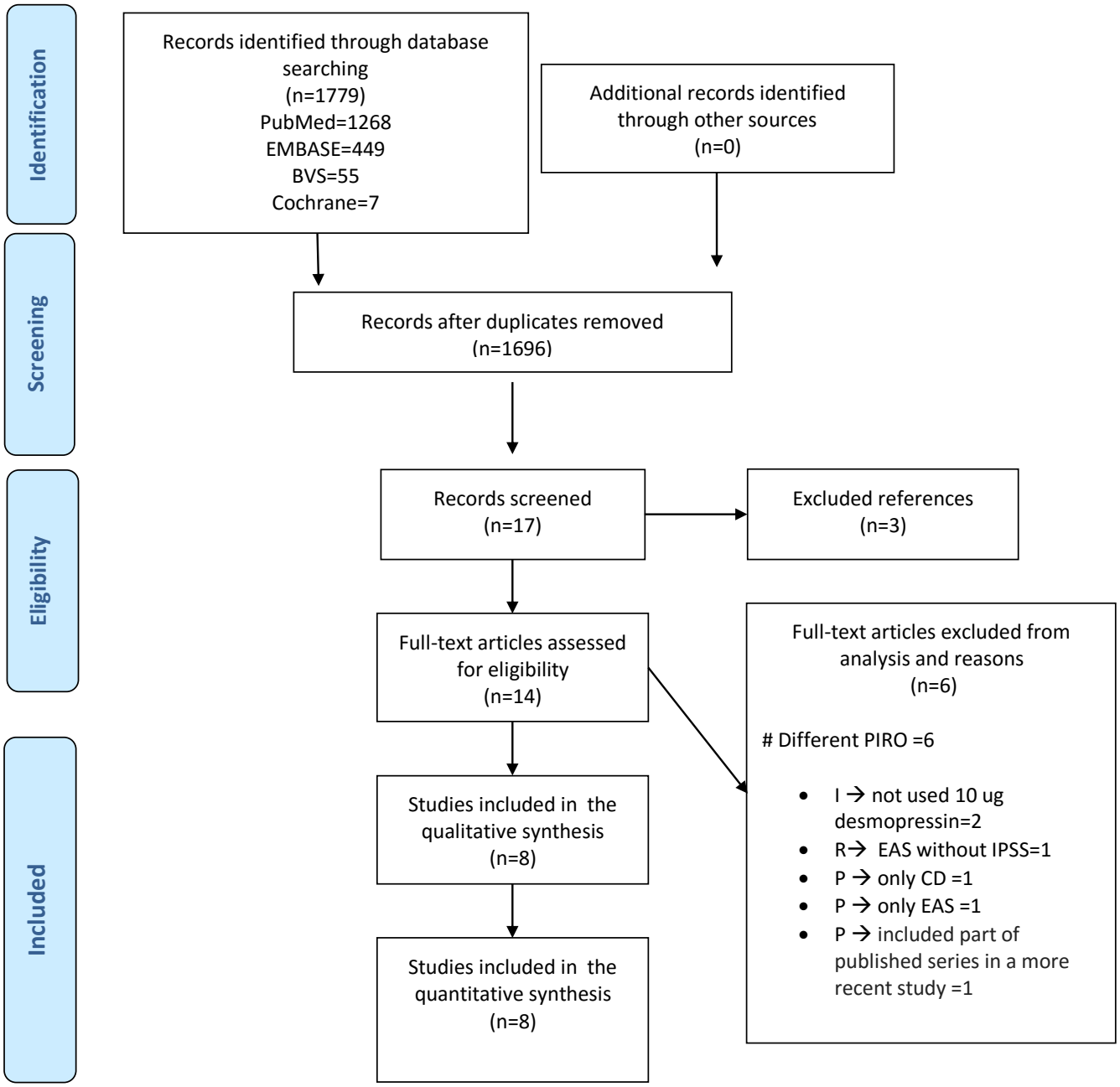

Figure 1. Flowchart for identifying eligible studies. BVS=Biblioteca Virtual da Saúde; CRH=corticotropin releasing hormone; CD=Cushing disease; EAS=ectopic ACTH syndrome; I=index test; IPSS=inferior petrosal sinus sampling; O=outcomes; P=patients; R=reference test.

Figure 2. Risk of bias and applicability: authors' judgment on each domain for each included study

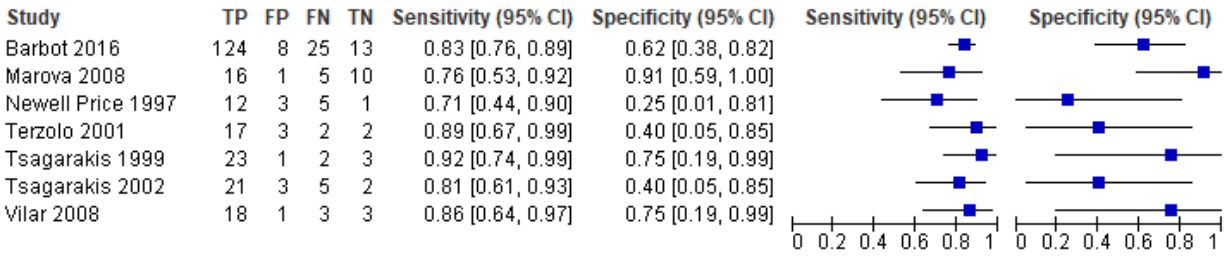

Figure 3. Forest plot of sensitivity and specificity considering ACTH percent increment after DDAVP test. The figure shows the estimated sensitivity and specificity of the study (blue square) and its 95% confidence interval (black horizontal line).

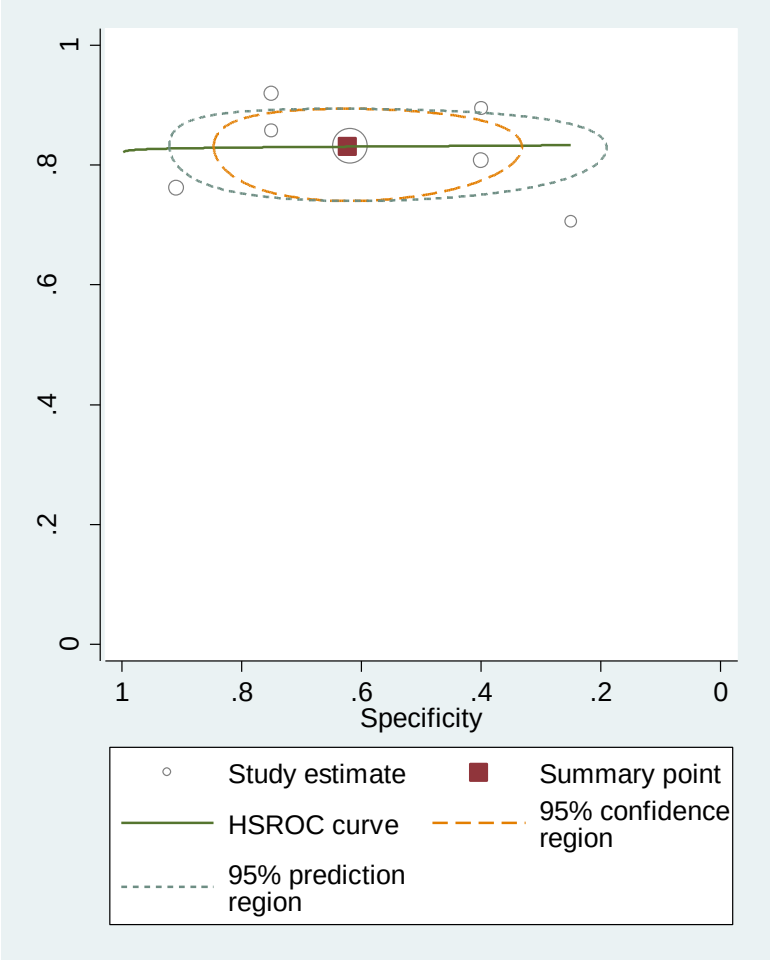

Figure 4. Summary ROC plots from Stata from fitting the hierarchical model to ACTH percent increment

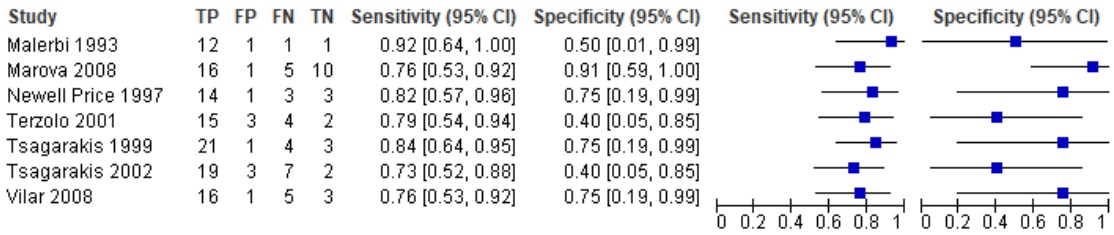

Figure 5. Forest plot of sensitivity and specificity considering cortisol percent increment after DDAVP test. The figure shows the estimated sensitivity and specificity of the study (blue square) and its 95% confidence interval (black horizontal line).

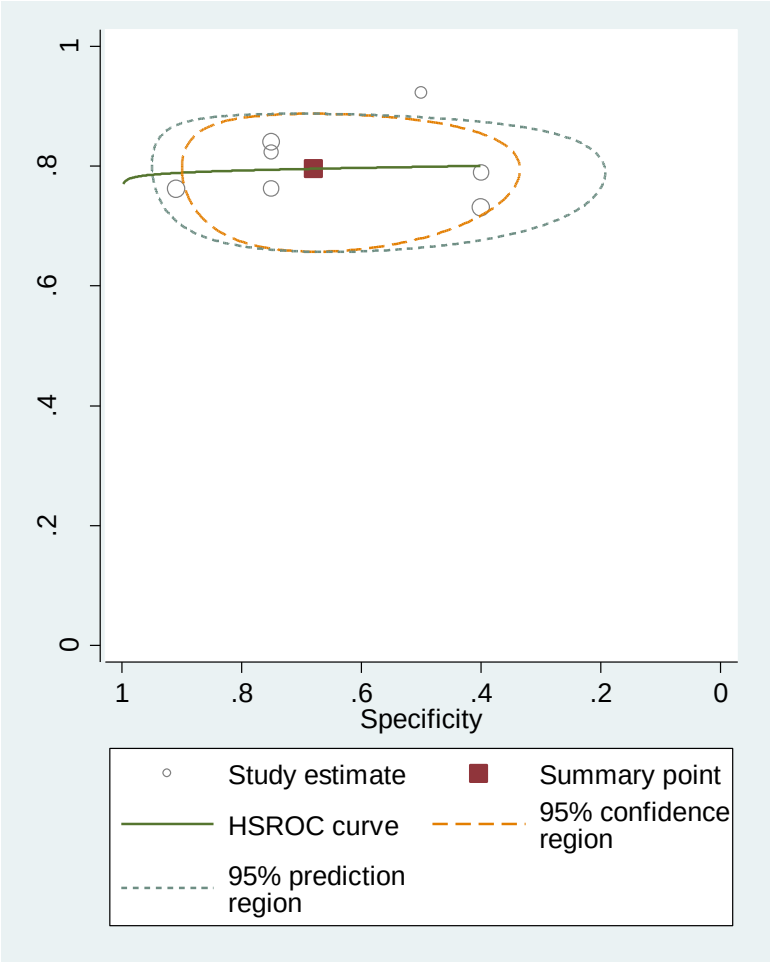

Figure 6. Summary ROC plots from Stata from fitting the hierarchical model to cortisol percent increment.

APPENDIX

Appendix 1 - Research Strategy

PUBMED – 10/01/2019

#1 "Pituitary ACTH Hypersecretion"[Mesh] OR (ACTH Hypersecretion, Pituitary) OR (Hypersecretion, Pituitary ACTH) OR (Cushing Disease, Pituitary) OR (Cushing Diseases, Pituitary) OR (Pituitary Cushing Disease) OR (Pituitary Cushing Diseases) OR (Pituitary-Dependant Hypercortisolism Disorder) OR (Hypercortisolism Disorder, Pituitary-Dependant) OR (Hypercortisolism Disorders, Pituitary-Dependant) OR (Pituitary Dependant Hypercortisolism Disorder) OR (Pituitary-Dependant Hypercortisolism Disorders) OR (Pituitary-Dependant Cushing Syndrome) OR (Cushing Syndrome, Pituitary-Dependant) OR (Pituitary Dependant Cushing Syndrome) OR (Pituitary-Dependant Hypercortisolism) OR (Hypercortisolism, Pituitary-Dependant) OR (Hypercortisolisms, Pituitary-Dependant) OR (Pituitary Dependant Hypercortisolism) OR (Pituitary-Dependant Hypercortisolisms) OR (Cushing Disease) OR (Disease, Cushing) OR (Pituitary Cushing Syndrome) OR (Cushing Syndrome, Pituitary) OR (Inappropriate ACTH Secretion Syndrome) OR (Inappropriate Adrenocorticotropic Hormone Secretion) OR (Adrenocorticotropic Hormone, Inappropriate Secretion) OR "Cushing Syndrome"[Mesh] OR (Syndrome, Cushing) OR (Cushing's Syndrome) OR (Syndrome, Cushing's) OR (Hypercortisolism) OR ACTH Secreting Pituitary Adenoma OR "ACTH-Secreting Pituitary Adenoma"[Mesh] OR (ACTH-Secreting Pituitary Adenomas) OR (Pituitary Adenomas, ACTH-Secreting) OR (Corticotroph Adenoma) OR (Adenoma, Corticotroph) OR (Adenomas, Corticotroph) OR (Corticotroph Adenomas) OR (Pituitary Corticotropin-Secreting Adenoma) OR (Corticotropin-Secreting Adenoma, Pituitary) OR (Corticotropin-Secreting Adenomas, Pituitary) OR (Pituitary Corticotropin Secreting Adenoma) OR (Pituitary Corticotropin-Secreting Adenomas) OR (ACTH-Producing Pituitary Adenoma) OR (ACTH Producing Pituitary Adenoma) OR (ACTH-Producing Pituitary Adenomas) OR (Pituitary Adenoma, ACTH-Producing) OR (Pituitary Adenomas, ACTH-Producing) OR (Pituitary Adenoma, ACTH-Secreting) OR (Pituitary Adenoma, ACTH Secreting)

#2 "Deamino Arginine Vasopressin"[Mesh] OR (Vasopressin, Deamino Arginine) OR (Arginine Vasopressin, Deamino) OR (Desmopressin) OR (1-Deamino-8-D-arginine Vasopressin) OR (Vasopressin, 1-Deamino-8-D-arginine) OR (1-Desamino-8-arginine Vasopressin) OR (Vasopressin, 1-Desamino-8-arginine) OR (Adiuretin SD) OR (Apo-

Desmopressin) OR (Apotex Brand of Deamino Arginine Vasopressin) OR (DDAVP) OR (Desmospray) OR (Octostim) OR (Ferring Brand 1 of Desmopressin Acetate) OR (Octim) OR (Desmopressine Ferring) OR (Ferring, Desmopressine) OR (Desmotabs) OR (Nocutil) OR (Norgine Brand of Desmopressin Acetate) OR (Hoyer Brand of Desmopressin Acetate) OR (Desmopressin Acetate) OR (Acetate, Desmopressin) OR (Desmopressin Monoacetate, Trihydrate) OR (Monoacetate, Trihydrate Desmopressin) OR (Trihydrate Desmopressin Monoacetate) OR (Desmopressin Monoacetate) OR (Monoacetate, Desmopressin) OR (IQFA Brand of Desmopressin Acetate) OR (Minirin) OR (Minurin) OR (Ferring Brand 2 of Desmopressin Acetate) OR (Adiuretin) OR (Desmogalen) OR (Galen Brand of Desmopressin Acetate) OR (Ddavp test*) OR "Corticotropin-Releasing Hormone"[Mesh] OR (Corticotropin Releasing Hormone) OR (ACTH-Releasing Hormone) OR (ACTH Releasing Hormone) OR (Corticoliberin) OR (CRF-41) OR (Corticotropin-Releasing Factor-41) OR (Corticotropin Releasing Factor 41) OR (Corticotropin-Releasing Hormone-41) OR (Corticotropin Releasing Hormone 41) OR (CRF (ACTH)) OR (ACTH-Releasing Factor) OR (ACTH Releasing Factor) OR (Corticotropin-Releasing Factor) OR (Corticotropin Releasing Factor)

Total: 1268

EMBASE – 10/01/2019

'Cushing disease'/exp OR ‘adrenocortical hyperplasia, acth induced’ OR ‘corticotropin induced adrenocortical hyperplasia’ OR ‘Cushing disease’ OR ‘cushing syndrome, acth induced’ OR ‘Cushings disease’ OR ‘itsenko cushing disease’ OR ‘pituitary ACTH hypersecretion’ OR 'ACTH secreting adenoma'/exp OR ‘ACTH-secreting pituitary adenoma’ OR ‘ACTH producing adenoma’ OR ‘ACTH producing adenomas’ OR ‘ACTH producing pituitary adenoma’ OR ‘ACTH producing pituitary adenomas’ OR ‘ACTH producing pituitary tumor’ OR ‘ACTH producing pituitary tumors’ OR ‘ACTH producing pituitary tumour’ OR ‘ACTH producing pituitary tumours’ OR ‘ACTH producing tumor’ OR ‘ACTH producing tumors’ OR ‘ACTH producing tumour’ OR ‘ACTH producing tumours’ OR ‘ACTH secreting adenomas’ OR ‘ACTH secreting pituitary adenoma’ OR ‘ACTH secreting pituitary adenomas’ OR ‘ACTH secreting pituitary tumor’ OR ‘ACTH secreting pituitary tumors’ OR ‘ACTH secreting pituitary tumour’ OR ‘ACTH secreting pituitary tumours’ OR ‘ACTH secreting tumor’ OR ‘ACTH secreting tumors’ OR ‘ACTH secreting tumour’ OR ‘ACTH secreting tumours’ OR ‘adrenocorticotropic hormone secreting adenoma’ OR ‘corticotroph adenoma’ OR ‘corticotroph adenomas’ OR ‘corticotropinoma’ OR

‘corticotropinomas’

'desmopressin'/exp OR ‘(1 deamino 8 dextro arginine) vasopressin’ OR ‘1 deamine 8 d arginine vasopressin’ OR ‘1 deamino 8 d arginine vasopressin’ OR ‘1 deamino 8 dextro arginine vasopressin’ OR ‘1 desamino 8 d arginine vasopressin’ OR ‘8 (1 desaminoarginine) vasopressin’ OR ‘[1 deamino 8 d arginine] vasopressin’ OR ‘[1 deamino 8 dextro arginine] vasopressin’ OR ‘[deamino 8 cysteine d arginine] vasopressin’ OR ‘[deamino 8 cysteine dextro arginine] vasopressin’ OR ‘[deamino 8 dextro arginine] vasopressin’ OR ‘adin’ OR ‘adiuretin’ OR ‘adiuretin sd’ OR ‘adiuretin-sd’ OR ‘concentraid’ OR ‘d-void’ OR ‘dav ritter’ OR ‘DDAVP’ OR ’DDAVP (needs no refrigeration)’ OR ‘DDAVP desmopressin’ OR ‘DDAVP melt’ OR ‘DDAVP nasal’ OR ‘DDAVP rhinal tube’ OR ‘DDAVP tablets’ OR ‘deamino 8 dextro arginine vasopressin’ OR ‘deamino 8d arginine vasopressin’ OR ‘deamino dextro arginine vasopressin’ OR ‘deaminovasopressin [8 d arginine]’ OR ‘defirin' OR 'defirin melt’ OR ‘desmirin’ OR ‘desmomelt’ OR ‘desmopresina’ OR ‘desmopressin acetate’ OR 'desmopressin acetate (needs no refrigeration)’ OR ‘desmopressin acetate preservative free’ OR ‘desmopressin diacetate’ OR ‘desmopressin nasal solution’ OR ‘desmopressina’ OR ‘desmopressine’ OR ‘desmospray' OR ‘desmotab’ OR ‘desmotabs’ OR ‘desmotabs melt’ OR ‘desurin’ OR ‘emosint’ OR ‘enupresol’ OR ‘minirin’ OR ‘minirin DDAVP’ OR ‘minirin melt’ OR ‘minirin nasal spray’ OR ‘minirin rhinetten’ OR ‘minirin rhinyle’ OR ‘minirin spray’ OR ‘minirinette’ OR ‘minirinmelt’ OR ‘minrin’ OR ‘minurin’ OR ‘minurin flas’ OR ‘minurin gotas’ OR ‘miram’ OR ‘nictur’ OR ‘noctisson’ OR ‘nocturin’ OR ‘nocutil’ OR ‘nordurine’ OR ‘novidin’ OR ‘nucotil nasenspray’ OR ‘octim’ OR ‘octostim’ OR ‘octostim nasal spray’ OR ‘octostim spray’ OR ‘presinex’ OR ‘stimate’ OR ‘vasopressin 8 (1 desaminoarginine)’ OR ‘vasopressin’ OR ‘1 deamino 8 dextro arginine’ OR ‘vasopressin’ OR ‘deamino 8 dextro arginine’ OR ‘vasopressin [1 (3 mercaptopropionic acid) 8 dextro arginine]’ OR ‘vasopressin [1 deamino 8 dextro arginine]’ OR ‘vasopressin [deamino 8 cysteine dextro arginine]’ OR ‘vasopressin [deamino 8 d arginine]’ OR ‘vasopressin [deamino 8 dextro arginine]’ OR ‘vasopressin [deamino dextro arginine]' OR 'wetirin’

Total: 449

LILACS / IBECS/ MEDCARIB / BBO / BDENF (BVS – IAHX) – 10/01/2019

Descriptor in portuguese: Hipersecreção Hipofisária de ACTH

Synonyms in portuguese:

Hipersecreção de ACTH Hipofisária

Hipersecreção de ACTH Pituitária

Hipersecreção Pituitária de ACTH

Doença de Cushing

Síndrome da Secreção Inadequada de ACTH

Secreção Inadequada de Hormônio Adrenocorticotrópico

C10.228.140.617.738.250.725

C19.700.355.800

Descriptor in portuguese: Síndrome de Cushing

C19.053.800.367

Descriptor in portuguese: Desamino Arginina Vasopressina

Synonyms in portuguese:

Desmopressina

Desaminoarginina Vasopressina

D06.472.699.631.692.781.100.250

D12.644.400.900.100.250

D12.644.456.925.100.250

D12.644.548.691.692.781.100.250

D12.776.641.650.937.100.250

Search strategy

#1 MH:"Hipersecreção Hipofisária de ACTH" OR (Hipersecreção de ACTH Hipofisária) OR (Hipersecreção de ACTH Pituitária) OR (Hipersecreção Pituitária de ACTH) OR (Doença de Cushing) OR

(Síndrome da Secreção Inadequada de ACTH) OR (Secreção Inadequada de Hormônio Adrenocorticotrópico)

OR MH:C10.228.140.617.738.250.725$ OR MH:C19.700.355.800$

#2 MH:"Síndrome de Cushing" OR

MH:C19.053.800.367$

#3 MH:"Desamino Arginina Vasopressina" OR (Desmopressina) OR (Desaminoarginina Vasopressina)

OR MH: D06.472.699.631.692.781.100.250$ OR MH: D12.644.400.900.100.250$ OR MH: D12.644.456.925.100.250$

OR MH: D12.644.548.691.692.781.100.250$ OR MH: D12.776.641.650.937.100.250$

Total: 55

CENTRAL - COCHRANE – 10/01/2019

ID	Search	Hits
#1	MeSH descriptor: [Pituitary ACTH Hypersecretion] explode all trees	18
#2	MeSH descriptor: [Cushing Syndrome] explode all trees	88
#3	MeSH descriptor: [Deamino Arginine Vasopressin] explode all trees	345
#4	Cushing disease	312
#5	#1 or #2 or #4	352
#6	#3 and #5	7

Total: 7

CONCLUSÃO

Diante dos resultados obtidos nas duas revisões sistemáticas e meta-análises, concluímos que o teste da desmopressina apresenta boa acurácia em diferenciar pacientes portadores de DC daqueles com PC, principalmente aqueles com DC e cortisolúria considerada “leve”. As comparações indiretas não demonstraram diferença estatística entre os pontos de corte adotados para o ACTH: delta-ACTH > 4 pmol/L associado a cortisol sérico >331 nmol/L e delta-ACTH > 6 pmol/L. Entretanto, pela baixa qualidade na evidência obtida, portadores de PC pelos critérios propostos para o teste da desmopressina devem ser seguidos e retestados se alteração no quadro clínico para SC. Naqueles com síndrome de Cushing ACTH dependente, a especificidade do teste foi heterogênea e apesar da menor incerteza em relação à sensibilidade, os resultados sugeriram que cerca de 20% dos portadores de DC seriam perdidos pelo teste.