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VALIDAÇÃO DA TÉCNICA DE INFILTRAÇÃO INTRALESIONAL DE ANTIMONIATO DE MEGLUMINA PARA TRATAMENTO DE LEISHMANIOSE CUTÂNEA

Rosiana Estéfane da Silva

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Dissertação apresentada ao Programa de Pós Graduação em Ciências da Saúde do Instituto René Rachou, como requisito parcial para obtenção do título de Mestre em Ciências da Saúde – área de concentração: Doenças Infecto-Parasitárias e Crônicas não Transmissíveis.

Orientação: Dra. Gláucia Fernandes Cota

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RESUMO

INTRODUÇÃO: Leishmaniose cutânea (LC) é uma doença negligenciada que constitui grave problema de saúde pública. São poucas as opções disponíveis para o tratamento de LC, sendo o antimoniato de meglumina (AM) por via parenteral considerado a droga de primeira escolha. O desenvolvimento e validação de novas alternativas terapêuticas é prioridade, diante das poucas e tóxicas opções de tratamentos atualmente disponíveis. Em 2017, o Ministério da Saúde do Brasil incluiu a infiltração intralesional (IL) de AM como alternativa terapêutica para casos específicos, apesar da inexistência da padronização e validação do procedimento. OBJETIVO: elaborar e validar o procedimento operacional padrão (POP) para infiltração intralesional de AM para tratamento de LC localizada. MÉTODOS: A elaboração do POP iniciou-se com revisão da literatura e observação direta da execução do procedimento realizada por profissional experiente em centro de referência para tratamento de LC. Questões conflitantes sobre a técnica, identificadas nesta primeira etapa, foram resolvidas por consulta eletrônica a especialistas. O POP foi submetido à validação sob três perspectivas: validade de conteúdo, critério e constructo. A validação de conteúdo foi realizada através de inspeção formal computadorizada para a verificação dos seguintes aspectos: legibilidade, clareza, omissão, redundância e informações desnecessárias. Para a validação de critério e constructo, indicadores próprios foram definidos e avaliados durante a execução de 118 procedimentos de IL AM, realizada por profissionais médicos treinados e não previamente treinados na técnica. Através da supervisão de um pesquisador observador, foram registrados o grau de adesão às instruções contidas no POP, o resultado obtido pelo procedimento e a tolerância informada pelo paciente, avaliada por escala visual analógica de dor. RESULTADOS: a mediana de duração do procedimento foi de 12 minutos, com sangramento leve em 96,6% dos casos, sendo a dor referida por 72% dos pacientes como leve. Em 66% das infiltrações observadas, constatou-se adesão completa ao roteiro de 10 itens para execução da técnica. Apesar disto, a saturação da lesão com a infiltração foi alcançada em 100% dos procedimentos, sugerindo robustez da técnica, que permite algum grau de modificação sem prejuízo no resultado obtido. CONCLUSÕES: a taxa de

adesão às instruções e de obtenção do resultado pretendido com o procedimento (saturação da lesão) foram altas entre profissionais com e sem experiência. A taxa de sangramento foi baixa e houve boa tolerância ao procedimento. Estas observações confirmam que a técnica do procedimento é reprodutível e confiável, podendo ser aplicada por profissionais sem treinamento prévio com alto grau de reprodutibilidade e segurança.

Palavras chaves: Antiomoniato de meglumina, Leishmaniose cutânea, terapia intralesional, validação.

ABSTRACT

INTRODUCTION: Cutaneous leishmaniasis (CL) is a neglected disease representing a serious public health problem. There are few options available for the treatment of CL, and parenteral meglumine antimoniate (MA) is still the first drug choice. The development and validation of new therapeutic alternatives is a priority given the few and toxic treatment options currently available for CL. In 2017, the Brazilian Ministry of Health included the MA intralesional infiltration (IL) as a therapeutic alternative for specific CL cases, despite the lack of standardization and validation of the procedure. OBJECTIVE: to elaborate and validate the standard operating procedure (SOP) for MA intralesional infiltration (MA-IL) for localized CL treatment. METHODS: The development of the SOP began with a review of the literature and a direct observation of the procedure performed by an experienced professional in a referral center for the treatment of CL. Conflicting questions about the technique, identified in this first stage, were resolved by electronic consultation to specialists. The SOP was submitted to validation from three perspectives: content, criterion and construct validity. Content validation was performed through formal computerized inspection to verify the following aspects: readability, clarity, omission, redundancy and unnecessary information. For the validation of criterion and construct, specific indicators were proposed and evaluated during the execution of 118 MA-IL procedures, performed by trained and not previously trained medical professionals. Through the supervision of an observer investigator, the degree of adherence to the instructions contained in the SOP, the result obtained by the procedure and the tolerance informed by the patient, evaluated by visual analogical pain scale, were recorded. RESULTS: The median duration of the procedure was 12 minutes, and mild bleeding was observed in 96.6% of the cases. Seventy two percent of the patients reported mild pain during the MA-IL. In 66% of the infiltrations, it was verified full adherence to the 10 items of the SOP. In spite of this, the saturation of the lesion with infiltration was achieved in 100% of the procedures, suggesting robustness of the technique, which allows some degree of modification without influencing the final result. CONCLUSIONS: the rate of adherence to the instructions and the achievement of the desired result with the

procedure (lesion saturation) were high among experienced and non-experienced professionals. The bleeding rate was low and there was good tolerance to the procedure. These observations confirm that the MA-IL procedure technique is reproducible and reliable and can be applied by professionals without previous training, with high reprodutibility and safety rates.

Keywords: Meglumine antimoniate, cutaneous leishmaniasis, intralesional infiltration, therapy, validation

LISTA DE FIGURAS

LISTA DE SIGLAS E ABREVIATURAS

AM - Antimoniato de meglumina

Anvisa – Agência Nacional de Vigilância Sanitária

CRL – Centro de Referência em Leishmanioses

DATASUS - Departamento de Informática do Sistema Único de Saúde

ECG – Eletrocardiograma

EV – Endovenoso

Fiocruz – Fundação Oswaldo Cruz

IL – Intralesional

IM – Intramuscular

INI-Fiocruz – Instituto Nacional de Infectologia Evandro Chagas da Fundação Oswaldo Cruz

IRR - Instituto René Rachou

LC – Leishmaniose cutânea

LM – Leishmaniose mucosa

LT – Leishmaniose tegumentar

MS – Ministério da Saúde

NNN LIT – Neal, Novy, Nicolle Liver Infusion Triptose

OMS – Organização Mundial da Saúde (WHO)

OPAS – Organização Pan-americana para Saúde

PCPP – Pesquisa Clínica e Políticas Públicas e Doenças Infecto-Parasitárias

PCR – Reação em cadeia da polimerase

POP – Procedimento Operacional Padrão

Rebec – Registro de estudos clínicos brasileiros

SINAN - Sistema de Informação de Agravos de Notificação

SUS – Sistema Único de Saúde

SUMÁRIO

1 INTRODUÇÃO

Leishmaniose tegumentar (LT) constitui-se em doença tropical negligenciada que provoca lesões de pele e em vias respiratória e digestivas altas - formas cutânea e mucosa (LC/LM), com potencial para deixar cicatrizes para toda a vida. Representa grave problema de saúde pública em 85 países em todo o mundo, inclusive nas Américas, onde dezessete países relataram 48.915 casos à Organização Pan-Americana da Saúde (OPAS) só em 2016. Os maiores números foram registrados pelo Brasil (12.690), seguido por Colômbia (10.966), Nicarágua (5.423) e Peru (7.271), que juntos respondem por 74,3% do total de casos na região (PAHO/WHO, 2018). A doença, que tem LC como sua forma mais frequente *(*ALVAR et al., 2012), é causada por protozoários do gênero *Leishmania,* transmitidos pela picada das fêmeas de flebotomíneos infectadas.

No Brasil, são aproximadamente 20.000 casos a cada ano, distribuídos amplamente por quase todo o território nacional, com transmissão principalmente focal. Em números oficiais, segundo dados do Sistema de Informação de Agravos de Notificação (SINAN), foram confirmados 119.394 casos de LT entre os anos de 2012 a 2017, 94,5% deles com a forma cutânea da doença (BRASIL, 2018). São perceptíveis as mudanças epidemiológicas apresentadas pela LT nos últimos anos, especialmente sua progressiva ocorrência em regiões periurbanas. As maiores taxas de incidência ocorrem em pacientes adultos, masculinos, na faixa etária produtiva entre 20 e 59 anos. Ressalta-se que a doença pode ser considerada ocupacional, impactando negativamente no campo social e econômico, uma vez que acomete preferencialmente indivíduos com atividades profissionais ligadas à agropecuária, mineração e extrativismo (TEMPONI et al., 2018).

São poucas as opções disponíveis para o tratamento de LT em todo o mundo. Além de arsenal reduzido e, em sua grande parte, exigindo administração parenteral exclusiva, são tratamentos associados a efeitos colaterais graves e várias contraindicações ao uso. O antimoniato de meglumina (AM), derivado pentavalente de antimônio disponível nas Américas, constitui-se ainda em medicamento de primeira escolha adotado pelo Ministério da Saúde (MS) no Brasil (BRASIL, 2017),

preconizado por via intramuscular (IM), endovenosa (EV) e, muito recentemente, também por infiltração intralesional. Com indicação principalmente consagrada pelo uso, tem efeitos adversos graves e bem conhecidos: toxicidades cardíaca, hepática, pancreática, renal e do sistema musculoesquelético, o que torna seu uso contraindicado em diversos grupos de pacientes com comorbidades.

De custo elevado e dados de eficácia em LT ainda escassos segundo Reveiz et al (2013), anfotericina B lipossomal encontra-se recomendada no Brasil para casos específicos como: portadores de insuficiência cardíaca, renal e hepática, transplantados, gestantes e maiores de 50 anos. Esta alternativa terapêutica tem como inconvenientes a necessidade de administração por via endovenosa exclusiva, o que implica na disponibilidade de ambiente hospitalar, além dos eventos adversos representados por reações associados à administração (febre, tremores, lombalgia), mas principalmente os distúrbios eletrolíticos e a toxicidade renal. Por fim, a pentamidina está indicada como primeira escolha em regiões onde predomina a infecção por *Leishmania guyanensis,* o que ocorre principalmente na região norte do país. Seus principais efeitos colaterais estão relacionados ao descontrole glicêmico (hiper e hipoglicemia), além de comprometimento pancreático, renal e cardíaco, leucopenia, trombocitopenia, hipocalcemia e choque anafilático (BRASIL, 2017).

Neste cenário de poucas opções terapêuticas e alta toxicidade, o desenvolvimento e validação de novas alternativas terapêuticas, incluindo abordagens locais aplicáveis à LC, são considerados prioridade. Dentre estas opções consideradas não sistêmicas, a infiltração intralesional de antimoniato de meglumina é a modalidade com mais experiência acumulada nas Américas e com a maior facilidade de implementação, por não exigir a aquisição de equipamentos específicos e utilizar medicação registrada e disponível no Brasil. Trata-se de abordagem já incluída, em 2013, pela Organização Pan-Americana de Saúde (OPAS, 2013) e recentemente, em 2017, pelo Ministério da Saúde do Brasil (BRASIL, 2017), entre as opções de tratamento para LC. Porém, ainda que já esteja recomendada, a técnica de infiltração intralesional não se encontra padronizada e validada. Apesar de abordagem promissora, a variabilidade no procedimento de infiltração dificulta a avaliação criteriosa de seus resultados, exigência da boa prática assistencial. Do ponto de vista operacional, considerando a ampla distribuição da doença e a heterogeneidade da infraestrutura em saúde instalada nas diversas regiões do Brasil, dificuldades relacionadas a inexistência de padronização do procedimento podem ser

antecipadas na implementação desta nova modalidade terapêutica, com risco de comprometer sua aceitação pelos profissionais de saúde, além da segurança dos pacientes. A infiltração intralesional para tratamento de LC é, antes de tudo, um procedimento médico e como tal requer padronização e validação, ou seja, avaliação sistemática do procedimento como método terapêutico de forma a determinar sua reprodutibilidade e capacidade de gerar um resultado em conformidade com o objetivo pretendido.

O Centro de Referência em Leishmanioses (CRL) do Instituto René Rachou (IRR) tem como missão produzir conhecimento aplicado, com foco nas doenças de relevância social no Brasil, e finalidade de subsidiar políticas públicas nacionais. Em consonância com esta missão, o desenvolvimento de alternativas terapêuticas, incluindo tratamentos locais para LC com menor potencial de toxicidade, é considerado uma prioridade. No presente estudo, procedimento operacional padrão (POP) para execução da infiltração intralesional de antimoniato de meglumina para tratamento de LC é proposto e validado com base na teoria psicométrica, tendo como critérios de avaliação os parâmetros de correção do roteiro instrutivo e de reprodutibilidade, qualidade do resultado, segurança e tolerância dos usuários ao procedimento.

2 OBJETIVOS

2.1 Objetivo geral

Elaborar e validar o procedimento operacional padrão para infiltração intralesional de antimoniato de meglumina para tratamento de leishmaniose cutânea localizada.

2.2 Objetivos específicos

1 Elaborar roteiro de ações sequenciais a compor o procedimento operacional padrão para o procedimento de infiltração intralesional de antimoniato de meglumina;

2 Verificar a adequação do procedimento operacional padrão, através da inspeção formal computadorizada;

3 Validar a técnica de infiltração intralesional de antimoniato de meglumina em pacientes com leishmaniose cutânea localizada sob os domínios da reprodutibilidade do método, qualidade do resultado, segurança do procedimento e tolerância por parte do paciente.

3 REVISÃO DA LITERATURA

3.1 Epidemiologia e transmissão da leishmaniose tegumentar

LT é uma doença infecciosa não contagiosa, provocada por protozoários pertencentes à família *Trypanosomatidae,* gênero *Leishmania, e* manifesta clinicamente por lesões na pele e mucosas. A infecção ocorre através da picada das fêmeas de flebotomíneos infectadas e o período de incubação da doença pode variar de duas semanas a dois anos, com média de dois a três meses. A doença possui ampla distribuição geográfica mundial, incluído o continente americano, onde existem relatos de casos desde o extremo sul dos Estados Unidos até o norte da Argentina, com exceção do Chile e do Uruguai (BRASIL, 2017).

É uma das endemias de maior importância em saúde pública no Brasil, distribuída em quase todo o território nacional, onde são descritos três padrões epidemiológicos, nomeadamente o silvestre, o ocupacional/recreativo e o rural/periurbano (BRASIL, 2017). O padrão silvestre de transmissão ocorre principalmente em áreas de vegetação primária, onde a infecção pode ser considerada uma zoonose de animais silvestres. Já a transmissão associada à atividade laboral ou de lazer está relacionado à exploração de matas e florestas, seja para atividade agropecuária, extrativismo ou ecoturismo. Por sua vez, o padrão rural/periurbano está ligado ao processo migratório e ocupação de encostas, frequentemente associado a matas secundárias ou residuais.

Segundo TEMPONI et al (2018), em uma análise do padrão de distribuição da LT no Brasil, a maioria dos casos da doença ocorre em pacientes do sexo masculino em idade produtiva e envolvidos com atividades laborais em áreas de desmatamento e/ou reflorestamento, especialmente trabalhadores dedicados às práticas agrícolas, extração de madeira e petróleo, construção de estradas, colheita, caça, pesca, mineração, atividades de pesquisa em florestas tropicais, loteamentos, e moradores nas proximidades de florestas. São também considerados sob risco de infecção populações vivendo em baixas condições socioeconômicas e sanitárias, o que pode ser um indicador de transmissão intra e peridomiciliar.

Nas Américas, são atualmente reconhecidas 12 espécies dermotrópicas de *Leishmania* causadoras de doença humana. No Brasil, já foram identificadas sete espécies, sendo seis do subgênero *Viannia* e uma do subgênero *Leishmania*

(BRASIL, 2017), cuja relevância encontra-se no potencial destas espécies em gerar diferentes manifestações clínicas e respostas terapêuticas às drogas disponíveis (WHO, 2010). *L. (V.) braziliensis* está presente em basicamente todo território brasileiro e constitui-se na principal espécie causadora de LC no Brasil, o que se reveste de importância adicional diante do seu potencial em causar a forma mucosa tardia, variação mais grave da doença (REIS et al., 2008).

O ciclo biológico da *Leishmania* inclui um vetor invertebrado e um hospedeiro vertebrado, podendo o parasita apresentar-se sob diferentes formas (amastigoa e promastigota), na dependência da fase do ciclo. A forma amastigota constitui-se em estrutura ovalada e sem flagelo, sendo encontrada no interior de células dos hospedeiros vertebrados. Já a forma promastigota, infectante, é alongada e flagelada, sendo encontrada no tubo digestivo dos insetos vetores. Grande variedade de mamíferos constitui a lista de hospedeiros vertebrados das *Leishmanias*, alguns domésticos (canídeos, felídeos e equídeos) e outros silvestres e sinantrópicos (marsupiais, edentados, quirópteros e canídeos silvestres), não havendo consenso sobre qual seria o principal reservatório no ciclo da LT no Brasil (BRASIL, 2017).

A transmissão da *Leishmania* ocorre durante repasto sanguíneo de fêmeas de flebotomíneos. São vetores pertencentes à Ordem Díptera, Família *Psychodidae,* Subfamília *Phlebotominae,* Gênero *Lutzomyia* e conhecidos popularmente, dependendo da região geográfica, como mosquito-palha, tatuquira, birigui. No Brasil, as principais espécies envolvidas na transmissão da LT são: *Lutzomyia flaviscutellata, Lu. whitmani, Lu. umbratilis, Lu. intermedia, Lu. wellcomei e Lu. Migonei*. A transmissão da doença, inclusive para o homem, hospedeiro acidental, se dá pela inoculação da forma extracelular promastigota na pele do hospedeiro, que em seguida é fagocitada por macrófagos, onde se transformam em amastigotas (BRASIL, 2017; FERREIRA; FORONDA; SCHUMAKER, 2003).

3.1.1 Principais variantes clínicas de LT

As manifestações de LT dependem da espécie de *Leishmania* infectante e da constituição genética e imunológica do hospedeiro. Utilizando o critério clínico proposto pelo Manual de Vigilância da Leishmaniose Tegumentar produzido pelo

Ministério da Saúde do Brasil (BRASIL, 2017), é possível identificar as formas cutânea e mucosa, detalhadas a seguir.

3.1.2 Formas cutâneas da LT

Caracterizam-se pelo acometimento exclusivo da pele, distinguindo-se entre si pelo número de lesões de pele e morfologia da lesão essencial, seja em função da espécie de *Leishmania,* seja pela condição imunológica do hospedeiro.

- **LC localizada:** a lesão frequentemente é localizada em áreas expostas do corpo, como face, braços e pernas. Inicia-se como uma mácula que pode durar de um a dois dias após a picada, evoluindo para uma pápula ou nódulo com tendência a ulcerar. Na maioria das vezes, a úlcera é indolor, com formato ovalado e/ou arredondado, com tamanho que pode variar de milímetros a alguns centímetros, tendo fundo eritematoso, infiltrado e de consistência firme, bordas bem delimitadas e elevadas, acompanhada ou não por linfoadenomegalia satélite. A forma cutânea localizada apresenta um amplo polimorfismo, podendo ser encontradas formas clínicas como impetigóide, liquenóide, tuberculosa ou lupóide, nodular, vegetante e ectimatóide, além das forma espotricóide (GONTIJO; CARVALHO, 2003). Representa a maior parte dos casos de LC notificados no Brasil, correspondendo a 78%, 61,7% e 71% dos casos em estudos realizados no Acre (SILVA-NUNES et al., 2008), Mato Grosso do Sul (MURBACK et al*.,* 2011) e Paraná (PONTELLO-JR et al., 2013), respectivamente.

- **LC recidiva cútis:** caracterizada pelo reinício da atividade inflamatória na periferia de uma lesão de pele já cicatrizada, tipicamente são pequenas pápulas e vesículas localizadas principalmente nas bordas de uma lesão cujo centro mantém-se epitelizado (GOTO; LINDOSO, 2010).

- **LC difusa:** trata-se de manifestação rara e de caráter disseminado, caracteriza-se pela formação de placas e nódulos não ulcerados que podem ser numerosos, difusamente distribuídos pelo corpo e caracterizados histologicamente por intenso infiltrado inflamatório e abundância de parasitos, do ponto de vista

clínico, apresenta refratariedade aos tratamentos disponíveis. No Brasil, o principal agente etiológico da forma difusa é *L. (L) amazonensis.*

- **LC disseminada:** caracteriza-se por múltiplas lesões em vários seguimentos corporais, de aspecto acneiforme, papular e, em alguns casos, com acometimento mucoso associado (GOTO; LINDOSO, 2010). Corresponde 2% dos casos notificados no Brasil, sendo as duas principais espécies envolvidas *Leishmania (V.) braziliensis* e *Leishmania (L.) amazonensis.*

3.1.3 Formas mucosas de LT

Trata-se de manifestação classicamente atribuída a complicação tardia da infecção cutânea, embora também descrita em pacientes sem cicatriz ou histórico da lesão de pele, representando em torno de 3-5% do total de casos de LT notificados anualmente (BRASIL, 2018). A forma clássica, que é considerada a forma mais mórbida de LT, caracteriza-se pelo comprometimento frequentemente tardio e isolado da mucosa de vias aéreas altas, tendo o septo nasal como o sítio mais acometido. Resultante da disseminação hematogênica e linfática dos parasitos do tecido cutâneo para a mucosa nasal, orofaringe, palatos, lábios, língua, laringe e, excepcionalmente, traqueia e árvore respiratória superior, podendo causar alterações funcionais e deformidades faciais, o que explica grande parte da morbidade da doença e seu impacto nas dimensões psicológica e social dos pacientes. Suas manifestações clínicas mais comuns são desconforto, ardor, obstrução nasal, aumento de secreção, formação de crostas e sangramento aos pequenos traumatismos. Estima-se que 90% dos casos ocorram em até dez anos da primo-infecção, sendo que destes, 50% podem ocorrer nos primeiros dois anos. As variedades clínicas da LM são:

- **forma mucosa tardia**: apresentação mais comum, caracteriza-se pelo comprometimento isolado de superfície mucosa anos após episódio de LC, tem evolução insidiosa, progressiva e destrutiva;
- **mucosa indeterminada**: variante da forma mucosa tardia, com a diferença de não haver histórico de LC prévia, sendo atribuída a infecções subclínicas ou

lesões pequenas não ulceradas e de evolução rápida que teriam passado despercebidas sem deixar cicatrizes perceptíveis;

- **mucosa concomitante**: caracterizada pela presença de lesão mucosa ocorrendo simultaneamente mas não contígua à lesão cutânea;
- **mucosa contígua**: caracterizada pela presença de lesão mucosa ocorrendo simultânea e contiguamente à lesão cutânea, é atribuída a propagação direta de lesão de pele;
- **mucosa primária**: ocorre pela picada do vetor diretamente na mucosa ou semimucosa.

3.2 Diagnóstico de LT

O diagnóstico exclusivamente clínico de qualquer das variantes de LT é hoje considerado estratégia insuficiente diante da ampla gama de diagnósticos diferenciais com apresentação indistinguível. Por outro lado, a suspeita clínico-epidemiológica, baseada em manifestações sugestivas e, principalmente, no conhecimento da transmissão local da doença é a base da abordagem diagnóstica. Dentre os métodos laboratoriais complementares disponíveis para a confirmação etiológica, estão os parasitológicos, que incluem a pesquisa direta do parasita e representados pelo isolamento do parasita em meio de cultura e o método molecular, com destaque para a reação em cadeia da polimerase (PCR) (BRASIL, 2017), além da histologia e dos métodos imunológicos, representados pela sorologia e intradermorreação de Montenegro.

A pesquisa direta, seja pelo *imprint* ou pelo esfregaço, baseia-se na visualização da forma amastigota do parasita em material preparado em lâmina a partir de fragmentos retirados por biópsia e/ou escarificação da lesão, possui sensibilidade de 70 a 75% (GOTO; LINDOSO, 2010; ESPIR et al., 2016). É considerado como método de primeira escolha para o diagnóstico da LC por ser rápido, de baixo custo e fácil execução. No entanto, a chance de encontrar o parasito nas lâminas é inversamente proporcional ao tempo de surgimento das lesões e, na presença de infecção bacteriana secundária, há uma redução da positividade do exame (BRASIL, 2017). A sensibilidade da cultura em meio de cultivo Novy-MacNeal-Nicolle e *Liver Infusion Triptose* (NNNLIT) varia de 40 a 75% (ROMERO et al., 1999), sendo de modo geral considerada menor que a do *imprint*

(BRASIL, 2017; GOTO; LINDOSO, 2010), especialmente quando executada a partir de fragmento de biópsia de pele, cujo alto percentual de contaminação bacteriana reduz sua sensibilidade para menos de 50% (WEIGLE et al., 1987).

Diferentemente dos métodos parasitológicos, os métodos imunológicos como a Intradermo reação de Montenegro (IDRM) e os testes sorológicos são baseados na resposta imune do hospedeiro. Na IDRM, a positividade do exame consiste na presença de indução igual ou superior a 5 mm a ser mensurada 48 ou 72 horas após a inoculação de 0,1 ml do antígeno na face flexora do antebraço (BRASI, 2017, SILVA et al., 2007). Estima-se uma positividade de 84% e 100% para a forma LC e LM, respectivamente (BRASIL, 2017; OLIVEIRA et al., 2005), sendo caracteristicamente negativa na forma cutânea difusa. IDRM apresenta, contudo, baixa especificidade, sem diferenciar infecção passada de doença ativa. De nota, a produção do antígeno para a IDRM está interrompida no Brasil desde 2015, por inexistência de plataformas de produção que atendam todas as exigências legais para o cultivo do parasito e isolamento do antígeno. Por sua vez, os testes sorológicos, amplamente usados no diagnóstico da forma visceral de leishmaniose, tem seu papel ainda indefinido no diagnóstico da forma tegumentar da doença (RAMIRES-JR et al., 1995). Com desempenho variado, a reação de imunofluorescência indireta (RIFI), o ensaio imunoenzimático (ELISA) e a reação de imunoblot (Western Blot) já foram avaliados em diversas formas clínicas de LT, sempre em estudos pequenos e metodologicamente limitados, o que impede uma conclusão definitiva sobre a acurácia do método sorológico, especialmente para LC (GOMES et al*.,* 2014, DE VRIES et al; 2015).

Por fim, os métodos moleculares, especificamente a reação em cadeia da polimerase (PCR), têm sido descritos como de alto desempenho - sensibilidade entre 97,1% e 100% (GOTO; LINDOSO, 2010), além de úteis na identificação e caracterização genômica das espécies (GARCIA et al., 2005). Como desvantagens, são reconhecidos como de alto custo, além de exigirem a presença de profissional altamente qualificado (BENSOUSSAN et al., 2006). Nenhum *kit* molecular encontra-se registrado no Brasil para o diagnóstico da LC, mas diferentes testes produzidos por metodologia *in house* vem sendo usados em centros de referência para o diagnóstico da leishmaniose no país, com significativa variação metodológica (PEREIRA et al., 2008; GOMES et al., 2008). Mais recentemente, dois testes baseados na pesquisa de antígenos ou do DNA do parasito foram lançados no

mercado mundial, ambos ainda sem registro na Agência Nacional de Vigilância Sanitária (ANVISA). No teste produzido pela mesma indústria produtora de teste rápido para leishmaniose visceral, a *INBIOS International*, a imunocromatografia é utilizada para permitir a leitura rápida de uma reação baseada na detecção de antígenos. O teste exige a coleta de fragmento de biópsia e foi validado em estudo com número reduzido de amostras, em que apresentou sensibilidade de 100%. Também baseado em evidência clínica limitada e valendo-se de leitura em fita de cromatografia, teste baseado em amplificação de DNA tendo como alvo o gene 18S ribossomal já é produzido pela empresa belga *Coris BioConcept* (ESPINOSA et al., 2009).

3.3 Tratamento da leishmaniose cutânea no Brasil

As recomendações vigentes do Ministério da Saúde para o diagnóstico e o tratamento da LT foram atualizadas no Manual de Vigilância da Leishmaniose Tegumentar Americana publicado em 2017. As principais mudanças trazidas por este documento foram a incorporação da infiltração intralesional de antimoniato de meglumina, a ampliação das indicações para uso de anfotericina B lipossomal e a recomendação do uso adjuvante de pentoxifilina para o tratamento da forma mucosa (BRASIL, 2017).

O arsenal terapêutico atualmente disponível para o tratamento de LT é ainda muito limitado, permanecendo como primeira escolha no Brasil, como na maior parte dos países endêmicos, os derivados pentavalentes do antimônio. São compostos utilizados há mais de 50 anos e disponíveis em duas apresentações: antimoniato de meglumina e estibogluconato de sódio, apenas a primeira delas disponível no Brasil, sendo produzida pela SANOFI-AVENTIS e distribuída pelo Ministério da Saúde sob o nome comercial Glucantime®.

Alternativamente, para pacientes apresentando falha ou contraindicação ao uso de derivados de antimônio, anfotericina B em sua formulação lipossomal, é também disponibilizada pelo Ministério da Saúde do Brasil, embora represente uma alternativa de maior custo e sustentada por escassa evidência de eficácia na LT. Por fim, a pentamidina encontra-se atualmente recomendada como primeira escolha para todas as formas clínicas causadas pela *L. guyanensis*, prevalente na região norte do país. Outras abordagens terapêuticas tais como paromomicina, miltefosina,

crioterapia e termoterapia ainda não são formalmente recomendadas no Brasil (BRASIL, 2017).

A resposta terapêutica ao tratamento da leishmaniose é influenciada por múltiplos fatores, incluindo fatores farmacológicos, o estado imunológico do hospedeiro e a espécie de *Leishmania*. Esses fatores dificultam a correlação entre resultados clínicos e padrão de suscetibilidade/resistência ao medicamento (LLANOS-CUENTAS et al., 2008). Por outro lado, falha terapêutica tem sido associada a alguns fatores, dentre eles duração, número e extensão de lesões, idade do paciente, espécie envolvida e presença de infecção helmíntica concomitante (O'NEAL et al., 2007) .

Uma meta-análise incluindo 1150 pacientes com LC nas Américas observou taxa de cura similar, em torno 76%, com antimoniais pentavalentes e pentamidina (TUON et al., 2008). Não foram observadas diferenças de eficácia relacionada às diferentes espécies de *Leishmania* (embora a maioria das infecções fosse devida a *L.V. braziliensis*). Também em relação ao tratamento com antimônio, diferença de eficácia entre regiões foi observada, com maiores taxas de cura na Colômbia em relação às observadas no Brasil (91% *versus* 71%, respectivamente). Duas outras revisões, acrescentando a evidência reunida até 2012, foram posteriormente publicadas, sem mudança significativa nas conclusões anteriores (GONZALES et al., 2009; REVEIZ et al., 2013).

Anfotericina B tem reconhecidamente alta eficácia contra *Leishmania*, mas taxas de cura com as diversas formulações são baseadas em séries de casos, não ensaios controlados. Em relação à formulação lipossomal, estudos não comparativos sugerem eficácia entre 80 a 85% (SOLOMON et al., 2007; SOLOMON et al*.,* 2013; MACHADO et al., 2015), mas revisão de casos em viajantes europeus revelou 46% de cura aos 3 meses (GUERY et al., 2017). Existem poucos estudos comparando anfotericina B com antimônio na LC (SOLOMON et al., 2013; NEVES et al., 2011; MOTTA; SAMPAIO, 2012). Em ensaio controlado comparando anfotericina B lipossomal em baixas doses (1,5 mg/kg/dia, cinco doses) com antimoniato de meglumina (20 mg/kg/dia, 20 doses) em 35 pacientes brasileiros com LC, as taxas de cura foram de 50% e 100%, respectivamente (MOTTA; SAMPAIO, 2012). Em outra série de casos, incluindo *L.(V). braziliensis*, 34 pacientes foram tratados com anfotericina B lipossomal (3 mg/kg/dia, seis doses) e 34 pacientes tratados com estibogluconato de sódio (20 mg/kg/dia por três semanas). Cura foi observada em

97% e 71% dos pacientes, respectivamente, sendo anfotericina B lipossomal melhor tolerada (SOLOMON, 2013).

De modo geral, todas as opções apresentam sérios inconvenientes, sejam relacionados à necessidade de administração injetável, que por si só exige a disponibilidade de uma série de condições estruturais, sejam relacionados à toxicidade relacionada a cada um deles.

A frequência de eventos adversos descritos durante o tratamento de LT nas Américas foi estimada em revisão da literatura publicada em 2011 por Oliveira et al. Em 32 artigos envolvendo 1866 pacientes, os efeitos adversos clínicos mais frequentemente relatados como associados ao tratamento com antimônio por via sistêmica foram dor no local da injeção (64%), artralgia/mialgia (48%), seguidos por cefaleia (23%), anorexia (19%) e distúrbios gastrointestinais (17%). Em relação às alterações laboratoriais, elevação de enzimas pancreáticas foi registrada em 59% dos artigos, seguida por elevação de enzimas hepáticas (43%) e alteração da repolarização ventricular (25%). Prolongamento do intervalo QTc foi descrito em 16% dos estudos e, alterações hematológicas, em torno de 7%. O pequeno número de estudos descrevendo toxicidade relacionada à anfotericina B no tratamento de LT identificados nesta revisão não permitiu uma compilação de resultados. Baseado em alguns relatos da literatura, os principais eventos adversos relacionados à anfotericina são nefrotoxicidade, hipocalemia, anemia, flebite e febre com calafrios relacionados à infusão. Efeitos colaterais adicionais associados à formulação lipossomal incluem dor torácica e no flanco durante a infusão, além de dispneia, urticária e rubor (WORTMANN et al*.,* 2010; THAKUR, 1998; MAHESHWARI et al., 2011; LANOS et al., 1991).

O risco de nefrotoxicidade associado à anfotericina B pode estar aumentado entre pacientes previamente tratados com antimoniais pentavalentes, parcialmente prevenido por sobrecarga salina (LHANOS, 1991). Além disso, o risco de prolongamento do intervalo QT com o uso de antimônio é aumentado pela hipocalemia induzida pela anfotericina B, que pode levar à arritmia cardíaca. Em função destas interações, um intervalo mínimo de ao menos 2 semanas entre os dois tratamentos (antimônio e anfotericina) deveria ser garantido (MAHESHWARI et al, 2011; THAKUR, 1998).

Já em relação aos pacientes tratados com pentamidina, os eventos mais relatados nas publicações foram anorexia (46%), dor no local da injeção (31%),

mialgia/artralgia (25%), tonteira (22%) e distúrbios gastrointestinais (21%). Surpreendentemente, embora hipo e hiperglicemia sejam complicações esperados com pentamidina, hipoglicemia foi observada em apenas dois dos 93 casos tratados (2,4%), um deles grave (SOTO-MANCIPE et al.,1993; SOTO et al., 1994). Nenhum caso de diabetes foi relatado. Por outro lado, uma alta frequência de rabdomiólise foi relatada em um dos estudos; entretanto, os autores usaram apenas a dosagem de creatinofosfoquinase alterada, entre o segundo e o décimo quinto dia após o tratamento, como critério diagnóstico (DELOBEL e PRADINAUD, 2003). Os efeitos adversos associados à miltefosina foram vômitos, náuseas, cinetose, cefaleia, diarreia e aumento discreto a moderado das aminotransferases e creatinina.

3.3.1 Infiltração intralesional de antimoniato de meglumina

Em 2010, a OMS recomendou a incorporação de tratamentos com abordagens locais e tópicas, incluindo a infiltração intralesional de AM, como opção terapêutica para o tratamento da leishmaniose cutânea também nas Américas. Em 2013, OPAS e, recentemente, em 2017, o Ministério da Saúde do Brasil também incluiram a infiltração intralesional de antimoniato de meglumina como alternativa terapêutica para casos selecionados de LC localizada. As vantagens potenciais da infiltração intralesional seriam o uso de doses totais mais baixas de antimônio, o que, em teoria, resultaria em menor toxicidade sistêmica, além de tratar-se de esquema com adminitração mais flexível, sem a necessidade de infusão diária, como ocorre habitualmente nos tratamentos sistêmicos.

A maior parte da evidência para o uso da infiltração intralesional de derivados de antimônio foi produzida no Velho Mundo, países como Irã e Afeganistão, onde o procedimento vem sendo empregado há várias décadas, como demonstrado por revisão sistemática realizada por Brito, Rabello e Cota (2017). Nesta revisão, que reuniu 40 estudos e uma população total de 5679 pacientes, apenas sete estudos foram realizados nas Américas. A revisão identificou grande variedade metodológica entre os estudos, mas foi possível estimar taxa de cura similar do tratamento IL em relação à terapia sistêmica com AM, em torno de 75%. Observou-se, contudo, descrição pobre da técnica de infiltração intralesional e grande heterogeneidade de regimes posológicos de terapia IL, no que se refere ao número e intervalo das

infiltrações e volume infiltrado. Da mesma forma, são poucas as informações disponíveis sobre a ocorrência de eventos adversos durante a terapia por infiltração intralesional (OLIVEIRA et al., 2011) e o risco de desenvolvimento de lesão mucosa tardia (VASCONCELOS et al., 2012) após tratamento IL com AM. Em relação à experiência já descrita nas Américas com a abordagem intralesional, segue breve descrição dos estudos já publicados.

1. Gadelha et al. (1990): revisão retrospectiva de casos tratados em Manaus, onde predomina a doença causada por *L guyanensis.* O total de 64 pacientes com 103 lesões receberam infiltração intralesional de AM, com taxa de cura de 93,7%. Segundo os autores, a técnica consistiu na "aplicação ao redor e no interior da lesão de 1 a 10 mL de AM, volume suficiente para preencher toda a lesão, não ultrapassando 10 mL por aplicação. O intervalo era inicialmente semanal e, com a melhora clínica, era aumentado para 10 a 15 dias. Apenas em lesões maiores que dois centímetros fazia-se anestesia prévia com infiltração de lidocaína". Neste estudo, foram realizadas em média 5,3 aplicações (variando de 4 a 10), sendo o volume médio infiltrado, por lesão, de 5,4 ml. Foram descritos eritema, edema e dor local em todos os casos. Urticária e lipotimia ocorreram em um paciente cada. Nesse trabalho, duas mulheres no 4° e 5° mês de gestação foram tratadas, os conceptos nasceram a termo e sem complicações.

2. Yepez e Scorza (1995): estudo prospectivo realizado na Venezuela com 97 pacientes com idade média de 25 anos e média de 1,4 lesões por paciente. Os pacientes foram distribuídos nos seguintes braços de tratamento: 1) 29 pacientes tratados com Glucantime® em infiltração intralesional, administrações semanais de 1 a 4 mL, taxa de cura de 83,3%; 2) 30 pacientes tratados com 2 mL de Glucantime® + 1 mL de lidocaína em infiltração intralesional semanal, taxa de cura de 100%; 3) 30 pacientes tratados com 1-3 mL de lidocaína 1% em infiltração semanal, taxa de cura de 93,3%. Em relação à técnica do procedimento, os autores mencionam a infiltração direcionada na borda das lesões e a infiltração até alcançar a palidez da lesão.

3. Oliveira-Neto et al, (1997): primeira publicação no tema de pesquisadores do Instituto Nacional de Infectologia Evandro Chagas da Fundação Oswaldo Cruz (INI-Fiocruz-RJ), grupo pioneiro na abordagem da infiltração intralesional de AM no Brasil, são apresentados os resultados dos 10 primeiros anos de experiência com a técnica, que incluiu 74 pacientes (com 82 lesões). A técnica informada para o procedimento incluía a infiltração prévia de anestésico seguida por "infiltração de AM através dos quatro pontos cardeais da lesão utilizando uma agulha de calibre 40 x 10 gauge movida em todas as direções até se alcançar toda a extensão da lesão, sendo o volume do medicamento variável de acordo com o tamanho da lesão". Dos 74 pacientes, 59 (79,7%) obtiveram epitelização completa das lesões em 90 dias a partir do início do tratamento, 12 pacientes (16,2%) foram considerados como falha terapêutica e três outros (4, 5%) não compareceram para avaliação de cura. Em 59 pacientes curados, foi realizada apenas uma infiltração. Após o tratamento, 43 (76,78%) desses pacientes foram acompanhados anualmente por um período de cinco anos, não sendo registrado recidiva ou desenvolvimento de lesão mucosa.

4. Vasconcelos et al. (2012): Outra publicação do grupo de pesquisadores do INI-Fiocruz-RJ, também uma revisão retrospectiva da experiência acumulada no serviço no período 2000 a 2006, desta vez relatando a evolução de 24 pacientes tratados pela abordagem intralesional por contraindicação à terapia sistêmica. O tratamento consistiu de 1 a 8 infiltrações, injetadas subcutaneamente, até saturar toda a lesão, com intervalos quinzenais, não sendo descrito o uso prévio de anestésico. Desse total, 20 pacientes (83%) obtiveram cura completa das lesões, em acompanhamento de até 60 meses, nenhum deles apresentou surgimento de lesão mucosa. Todos os pacientes durante o tratamento foram acompanhados com realização de avaliação clínica, exames

laboratoriais e eletrocardiograma (ECG) para avaliar toxicidade do tratamento, nenhum apresentou qualquer evento adverso sistêmico.

5. Soto et al., (2013): outro ensaio clínico randomizado realizado pelo mesmo grupo na Bolívia, com 80 pacientes com lesão única de até 900 mm^2 de área. Foram comparados três braços de tratamento para LC: Braço 1: 30 pacientes randomizados para o tratamento IL com AM, taxa de eficácia de 70%; Braço 2: 20 pacientes tratados com placebo, taxa de cura de 17%; Braço 3: 30 indivíduos submetidos à crioterapia, eficácia de 20%. As infiltrações de AM eram realizadas com uma periodicidade de 1, 3 e 5 dias, e antes de cada infiltração, os autores descrevem a realização de anestesia em quatro pontos da lesão, com posterior infiltração de AM em toda a lesão até alcançar a saturação.

6. Soto et al. (2016): trata-se de ensaio clínico realizado na Bolívia avaliando a eficácia da infiltração intralesional de AM em comparação com a infiltração intralesional de pentamidina para o tratamento de lesões únicas de LC por *L. (V.) braziliensis.* O estudo consistiu de duas etapas, na primeira, 90 pacientes foram randomizados para três braços de tratamento: a). IL AM (3 infiltrações durante 5 dias consecutivos, taxa de cura de 57%) e b). AM IL (cinco infiltrações em dias alternados, taxa de cura de 73%) e c). pentamidina IL por 3 dias (taxa de cura de 72%). Na segunda etapa do estudo foram incluídos 60 pacientes, 30 deles tratados com cinco infiltrações intralesionais de AM (taxa de cura de 67%) e 30 outros tratados com infiltração intralesional de pentamidina (taxa de cura de 73%). Nesse estudo os autores descrevem a aplicação prévia de anestésico em quatro pontos cardeais da lesão antes da realização do procedimento terapêutico. Segundo a técnica de infiltração informada, o objetivo do procedimento era levar a lesão ao estado de “saturação”.

7. Silva et al. (2016): revisão retrospectiva da experiência acumulada com a abordagem intralesional no período de 2008 a 2013 no Centro de

> Referência em Leishmanioses em Belo Horizonte, antes da padronização do procedimento no serviço. Foram descritos 31 pacientes, com idade média de 63 anos. Em média eram realizadas de uma a seis infiltrações, com intervalo médio de 15 dias e por um período de até 12 semanas, com uma média de 3 mL de volume infiltrado por sessão. A taxa de cura foi similar à descrita com a terapia sistêmica, de 70,9% (22/31) na avaliação parcial de 90 dias e 67,7% (21/31) na avaliação de cura final com 180 dias. Não houve relato de desenvolvimento de lesão em mucosa durante o seguimento.

A compilação da evidência disponível demonstra claramente a inexistência de padronização da técnica de infiltração intralesional de AM entre os estudos, além de grande heterogeneidade dos esquemas utilizados. São obstáculos para a reunião e comparação dos resultados e, em última análise, para a implementação da abordagem intralesional em larga escala, objetivos que só serão alcançados após a padronização da técnica do procedimento.

3.4 Processo de validação

Validação, segundo o 32*th* Report da OMS (WHO, 1992), é o ato documentado que atesta que qualquer procedimento, processo, equipamento, material, operação ou sistema realmente conduza aos resultados esperados. Estudos de validação de processos têm por objetivo avaliar se determinado processo consegue gerar produtos conformes. Resumidamente e de forma didática, valendo-se do exemplo da produção industrial, a metodologia consiste em obter uma amostra de produtos fabricados em condições normais de operação, avaliar a estabilidade estatística (ou previsibilidade) do processo e, determinar a capacidade deste processo gerar produtos dentro das especificações esperadas.

A Anvisa, através da resolução Resolução-RDC nº. 17, de 16 de abril de 2010, define que:

> *"a validação de processo consiste de evidência documentada que atesta com um alto grau de segurança que um processo específico produzirá um produto de forma consistente, que cumpra com as especificações pré-definidas e características de qualidade"* (BRASIL, 2010).

Essa definição é muito utilizada para fins regulatórios, especialmente no caso de produtos no meio industrial, principalmente na área de alimentos e farmacêutica. Diferentemente dos produtos na área da saúde, em que fica clara a necessidade de validação, para processos não se identifica um guia com orientações universais de como a validação deve ser conduzida. Parte desta dificuldade recai sobre a diversidade inerente aos processos, fazendo com que cada um requeira um conjunto de técnicas e ferramentas diferentes. Considerando o princípio geral da validação, no caso de processos, a lógica se baseia na aplicação de "critérios, parâmetros e metodologias que sejam cientificamente justificáveis e que demonstrem claramente que o processo produz resultados em conformidade com as especificações pré-estabelecidas" (BRASIL, 2006). Em outras palavras, processos na área da saúde precisam ter sua validade e confiabilidade atestada. Validade e confiabilidade são propriedades métricas, o que no caso de processos significa mensuração de parâmetros decorrentes da aprendizagem e capacidade de execução, habilidades psíquicas que envolvem comportamento e cognição. A validade de um instrumento ou teste busca mensurar o que se propõe a medir e a confiabilidade é determinada através da reprodução dos resultados obtidos por um determinado teste. Em relação à validade de testes comportamentais ou cognitivos, define que este é válido quando realmente de fato mede o que se propõe a mensurar (PASQUALI, 2009; BOLARINWA, 2015). A ciência que estuda e sistematiza a quantificação de variáveis psicológicas é a psicometria.

3.4.1 Teoria psicométrica

De acordo com Pasqualli (2009) O termo psicometria foi criado pelos psicólogos alemães Ernst Heinrich Weber e Gustav Fechner, em colaboração com Francis Galton, para designar testes desenvolvidos para a avaliação de processos mentais. Trata-se de método quantitativo baseado nos princípios fundamentais da ciência capaz de descrever, com maior precisão que a linguagem comum, determinados fenômenos advindos da mente humana. A psicometria passou então a

ser entendida como a teoria que sustenta a utilização de técnicas para a mensuração de habilidades mentais, muito utilizada em psicologia e educação. Em outras palavras, a psicometria busca entender e explicar o sentido que possuem os resultados dados por sujeitos quando submetidos a uma série de testes ou instrumentos de avaliação.

Do ponto de vista prático, com base na teoria psicométrica, fenômenos psicológicos podem ser medidos e analisados objetivamente através da utilização de instrumentos adequados, os testes psicométricos. São ferramentas capazes de reduzir os vieses subjetivos de avaliação do examinador, desde que este tenha completo domínio e conhecimento de sua aplicação e interpretação (SARTES e FORMIGONI, 2013). Frequentemente na área da saúde, tem-se utilizado ferramentas, como questionários, testes, protocolos e/ou escalas que buscam orientar a execução de procedimentos, verificar e mensurar fenômenos de interesse tanto para pesquisa quanto para fins assistenciais. É, portanto, imprescindível que essas ferramentas possuam validade, confiabilidade e fidedignidade para atestar seu resultado, evitando vieses que gerem desvios no processo e incorreções no resultado final, o que, dependendo da atividade, pode resultar em danos graves ao usuário do sistema de saúde (COLUCI et al., 2015 e PASQUALI; 2009),.

Segundo Coluci et al., (2015) e Pasquali (2009), o uso de instrumentos na prática são somente úteis e fidedignos se forem capazes de demonstrar robustez em seus resultados, quando apresentam boas propriedades psicométricas (KESZEI et al., 2010). E para atestar a robustez desses instrumentos, o processo de validação é, portanto, etapa imprescindível e anterior à implementação de novos instrumentos e processos na área da saúde, a fim de garantir sua credibilidade e confiabilidade (PASQUALI, 2009; MEDEIROS et al., 2015).

Neste sentido, entende-se como confiabilidade de um instrumento a sua capacidade em produzir, de forma consistente, o mesmo resultado entre executores diferentes (BELUCCI-JR; MATSUDA, 2012).

A primeira etapa da validação consiste na identificação de conjunto de medidas ou indicadores capazes de descrever acuradamente os fenômenos para que estes possam ser analisados estatisticamente. No caso dos processos, é preciso além de uma definição clara do resultado pretendido, da descrição objetiva de como se dará a verificação ou mensuração deste resultado. A determinação da validade das medidas se dá empiricamente e tem como base um exame sistemático

de abstrações conceituais, por meio de observação e mensuração de respostas que tentam explicar o fenômeno de interesse.

Em síntese, todo processo de validação busca garantir o isomorfismo, ou seja, a equivalência entre as propriedades do atributo psicológico e a representação deste objeto na forma de um instrumento de medida. Para atestar e garantir essas propriedades psicométricas, a validação avalia o processo sob três perspectivas, a saber: validação de conteúdo, validação de critério e validação de construto (LOBÃO e MENEZES, 2013).

Validade de conteúdo: analisa se um instrumento realmente cobre os diferentes aspectos do seu "processo" e não contém elementos que podem ser atribuídos a outros "processos". Nesta etapa, são avaliadas a presença no instrumento de ambiguidade, omissão, redundância, informação estranha.

Essa etapa do processo de validação refere-se ao julgamento da completude e correção do instrumento. Geralmente, a validade de conteúdo é composta por duas etapas, primeiro o desenvolvimento/construção do instrumento e, a seguir, julgamento e a análise desse por especialistas, que tem por objetivo avaliar se o conteúdo está adequado ao que se propõe (CRESTANI et al*.,* 2017).

A validade de conteúdo não é definida estatisticamente, não sendo expressa por um coeficiente de correlação. É nesta etapa em que, geralmente especialistas no assunto em questão (*experts)* avaliam a adequação dos itens que compõem o instrumento com o objetivo de checar se estes cumprem de fato sua finalidade de guiar ações específicas (RAYMUNDO, 2009). Em síntese, nesta etapa é avaliada a clareza e relevância de cada item do instrumento (ALEXANDRE; COLUCCI, 2011) e se os itens abordados são compreensíveis à população alvo em que o instrumento será aplicado. Como esta etapa frequentemente é realizada com a colaboração de especialistas, de forma intuitiva e baseada em sua experiência pessoal com o assunto, está muitas vezes exposta a alguma subjetividade.

Validade de critério: indica em que grau modificações no processo/executor influenciam o resultado, também chamada de estabilidade estatística, ou seja, consiste na avaliação do impacto de alterações em condições críticas durante o processo, no caso de um roteiro instrutivo, por exemplo, como a adesão à proposta de ações sequenciais e a experiência do profissional influenciam o resultado final obtido.

Pasquali (2009) define a validade de critério como o grau de eficácia do desempenho específico do instrumento, a ser medido através de técnicas independentes do próprio teste que se objetiva validar. De forma prática, a validade de critério se relaciona às pontuações alcançadas (ou resultado obtido) em comparação com aquelas obtidas através de outro instrumento/processo de avaliação (TERWEE et al., 2007). Dependendo do instrumento em validação, refere-se também ao resultado observado em caso de alteração de alguma condição relacionada à execução do processo. A validade de critério se subdivide em dois tipos: validade preditiva e validade concorrente, que diferem em relação ao momento em que as informações sobre as alterações no processo e no resultado são obtidas (PASQUALI, 2009). Tanto na validade preditiva quanto na validade concorrente, as medidas que avaliam o critério, devem ser alcançadas de forma independente (RAYMUNDO, 2009).

Validade de constructo: refere-se à demonstração de que o instrumento realmente produz aquilo que se propõe a produzir, ou seja, refere-se à robustez e tolerabilidade (BRASIL, 2003). Segundo Pasquali (2009), a validade de constructo é considerada a forma direta de mensurar a extensão em que a medida corresponde à construção teórica do fenômeno a ser avaliado. Dentro do processo de validação, a validade de constructo é o processo mais significante por mensurar e avaliar a atividade final de um instrumento (BOLARINWA, 2015).

Para Raymundo (2009) as evidências para esse tipo de validação são alcançadas fazendo uma série de estudos ou executando-se outros processos que atestem as propriedades do resultado. Alternativamente, podem ser realizados testes inter-relacionados de natureza teórica, valendo-se de princípios estatísticos, sendo que a constatação de conformidade com o previsto se dá, idealmente, através do acúmulo de diferentes evidências.

Grande parte da discussão inicial de validade foi expressa dentro de uma filosofia realista da ciência, em que a variável de interesse foi assumida como tendo um valor definido para o instrumento em análise, e o objetivo da medição era estimar o valor dessa variável com a maior precisão possível. Ou seja, a validade era definida em termos da precisão da estimativa. Na prática, essa visão de validação exigia alguma medida que era assumida para fornecer o valor "real" da variável de interesse, ou pelo menos aproximação deste valor "real". Dado tal critério, a validade poderia ser avaliada em termos de quão bem os resultados dos testes estimaram ou

previram este valor real, em termos de pontuações. Em síntese, a medida de critério era tomada como o valor do atributo de interesse, e o teste era considerado válido avaliando-se qualquer parâmetro para o qual existissem estimativas mensuráveis (KANE, 2001). Basicamente, a validade do critério, definido aqui em termos de "desempenhos de tarefas" era dada como certa, e os resultados dos testes deveriam ser validados em termos de escores. Este modelo baseado em critérios é bastante razoável e útil em muitos contextos, assumindo que alguma medida adequada de "critério" esteja disponível, tendo permitido o desenvolvimento de algumas análises muito sofisticadas para a mensuração da validade de um determinado instrumento, inclusive com o desenvolvimento de várias regras de decisão a serem empregados (CRONBACH E GLESER, 1965). Contudo, o problema com este modelo de avaliação baseado em escores é a necessidade de um parâmetro comparador bem definido e medida de critério comprovadamente válida, já que, em muitos casos, parâmetros outros aplicáveis não estão prontamente disponíveis. Além disto, mesmo que algum parâmetro possa ser identificado, frequentemente se encontra dificuldade em confirmar que este parâmetro seria confiável para a definição da propriedade em análise, situação muitas vezes denominada de regressão infinita ou influência da circularidade na comparação do teste. Uma maneira de sair desse dilema é empregar uma medida de critério envolvendo o desempenho desejado (ou algum resultado desejado) e interpretar as pontuações em termos do alcance desse tipo de resultado.

No início da década de 1950, o Comitê da Associação Americana de Psicologia e Testes Psicológicos achou necessário ampliar a atual definição de validade, a fim de acomodar as interpretações atribuídas às avaliações clínicas. Um subcomitê de dois membros, Paul Meehl e Robert Challman, introduziu então a noção e a terminologia da validade de construto, que foi incorporada às Recomendações Técnicas de 1954 (American Psychological Association, 1954), e desenvolvido por Cronbach e Meehl (1955). Estes autores propuseram o modelo da teoria hipotético-industrial (HD), que foi dominante no início de 1950 (SUPPE,1977) e que tratava as teorias como sistemas axiomáticos interpretados. Um conjunto de axiomas conectando determinados termos implicitamente definidos (os constructos teóricos) constitui o núcleo de uma teoria. Os axiomas são interpretados conectando alguns de seus termos às variáveis observáveis, através de "regras de correspondência", o que naturalmente pressupunha sempre a disponibilidade de

algumas variáveis observáveis. Uma vez interpretados, os axiomas podem ser usados para fazer previsões sobre as observações que então demonstram as relações entre variáveis, sendo essas leis empíricas sustentadas exatamente pela teoria (HEMPEL, 1965).

Em resumo, a validade segundo esta metodologia se baseia em termos de quão bem as pontuações satisfazem a teoria. Se as observações forem consistentes com a teoria, a validade da teoria e dos procedimentos de medição usados para estimar os construtos, definidos pela teoria, são ambos suportados. Se as observações não são consistentes com a teoria, alguma parte da rede seria rejeitada, o que por si só não é capaz de indicar se a falha está nos axiomas, nas regras de correspondência empregadas ou nos procedimentos escolhidos de medição.

Assim, resultados desta evolução da teoria de validação, as definições atuais de validade refletem os princípios gerais inerentes ao modelo de validade de constructo, mas descarta a ênfase nas teorias formais. Atualmente, o conceito mais aceito para validade é um julgamento integrado do grau em que a evidência empírica e o racional teórico suportam a adequação e a precisão das inferências e ações extraídas dos escores, ou de outros métodos de medida, obtidos por determinado instrumento em avaliação. Isto é, essa validação requer uma análise alargada de provas, com base numa declaração explícita da interpretação proposta. Também considera outras interpretações concorrentes, de modo a incluir todos os argumentos de validade.

Quatro aspectos desta visão atual são dignos de nota. Primeiro, a validade envolve uma avaliação da plausibilidade geral de uma proposta de interpretação dos resultados dos testes. É a interpretação (incluindo inferências e decisões) que é validada não o teste ou a pontuação do teste. Segundo, consistente com os princípios gerais que emergem da validade de construto, as definições atuais de validade (MESSICK, 1989) incorporaram a noção de que as interpretações propostas envolvem uma extensa análise de inferências e suposições. Este julgamento avaliativo inexoravelmente engloba a análise de adequação do objeto e do próprio ato de interpretar, estando então sujeito aos vícios inerentes às inferências usadas.

Terceiro, a aplicação dos métodos e principalmente das pontuações para uma finalidade específica exige análise criteriosa das consequências de seu uso.

Preocupações sobre as consequências deste uso são evidentes na definição de CURETON (1950). Embora não haja consenso ou recomendação de utilização, este aspecto tem recebido mais atenção (KANE, 2001). Ao menos um autor (POPHAM, 1997) sugeriu que os escores não deveriam desempenhar nenhum papel na validade.

Em quarto lugar, a validação é um processo de avaliação integrado e unificado e não simplesmente uma coleção de técnicas ou ferramentas. Assim, as inferências incluídas na interpretação devem ser especificadas; estas inferências e quaisquer suposições necessárias devem ser não apenas plausíveis, mas apoiadas por evidências e todos os componentes específicos devem ser inspecionados.

4 METODOLOGIA

O estudo foi desenvolvido em duas etapas sequenciais: primeiro a elaboração e, a seguir, a validação do procedimento operacional padrão (POP) para a realização de infiltração intralesional de antimoniato de meglumina. A validação foi executada através da inspeção formal do POP e da validação clínica da técnica proposta.

4.1 Local do estudo

Centro de Referência em Leishmanioses do Instituto René Rachou (IRR), Fiocruz, Belo Horizonte, Minas Gerais.

4.1.1 Aspectos éticos

O projeto foi submetido e aprovado pelo Comitê de Ética do Instituto René Rachou (IRR), Fiocruz (número de aprovação 1.136.132). Protocolo do estudo foi registrado na base de registro de estudos clínicos brasileiros (Rebec), sob o número RBR-44KG5X.

4.1.2 População do estudo

Para a fase de validação clínica do POP foi realizada com os primeiros 38 participantes incluídos no estudo RBR-44KG5X que avaliou a eficácia e segurança da infiltração intralesional de antimoniato de meglumina em pacientes de ambos os sexos e idade superior a 12 anos, com diagnóstico confirmado de infecção por *Leishmania, a*té três lesões cutâneas, sem acometimento mucoso.

4.2 Elaboração do POP

A elaboração inicial do POP seguiu três etapas sucessivas:

- Revisão na literatura sobre as descrições da técnica de infiltração intralesional de antimoniato de meglumina já publicadas;

- Observação da execução do procedimento realizado por profissional com experiencia na técnica;
- Consulta a comitê de especialistas.

4.2.1 Revisão da literatura

Realizou-se busca nas bases de dados MEDLINE e LILACS em julho de 2015 usando uma estratégia baseada nos principais indexadores do assunto combinados por operadores booleanos, como descrito na Figura 1. Não houve restrição de idioma, mas a pesquisa bibliográfica foi limitada a estudos publicados nos últimos 10 anos, usou-se o filtro "ensaio clínico". Estudos adicionais foram localizados por uma pesquisa manual usando referências dos artigos recuperados. Todos os estudos identificados foram lidos na íntegra com foco na descrição do procedimento de infiltração intralesional, especificamente: o uso ou não de anestesia; especificação da agulha utilizada, inclinação, direção e profundidade durante a infiltração; volume de droga infiltrado, critério usado para cessar a infiltração do medicamento.

FIGURA 1 - Estratégia de busca na literatura

"Leishmaniose Cutânea"

OR "Leishmaniasis, Cutaneous" OR "Leishmaniasis Cutánea" OR "Cutaneous Leishmaniasis") AND (MH:D01.268.513.124 OR Antimônio OR Antimony OR Antimonio OR MH: D02.033.800.813.550 OR Meglumina OR Meglumine OR MH: D02.241.081.844.322.060 OR "Gluconato de Antimônio e Sódio" OR "Antimony Sodium Gluconate" OR "Gluconato de Sodio Antimonio" OR MH:D27.505.954.122.250.100 OR Antiprotozoários OR "Antiprotozoal Agents" OR Antiprotozoarios OR "antimoniato de meglumina" OR "meglumine antimoniate")) AND (Infiltração OR Infiltración OR Infiltration OR intralesional), Validation.

4.2.2 Inspeção de procedimento executado por profissional experiente

Realizou-se observação direta do procedimento executado por um profissional com 5 anos de experiência na técnica de infiltração intralesional adotada

no CRL-IRR, com registro do passo-a-passo do procedimento por dois observadores independentes.

4.2.3 Consulta eletrônica a comitê de especialistas

Para resolver ações do procedimento que não foram completamente esclarecidas durante a revisão da literatura e observação do procedimento, ou que eram conflitantes nas etapas anteriores, todos os grupos de pesquisa com experiencia em ensaios clínicos em infiltração intralesional de antimoniato de meglumina identificados pela revisão da literatura foram contatados por via eletrônica e convidados a responder questionário específico. No caso de mais de uma publicação do mesmo grupo, o contato foi feito com o coordenador do grupo, muitas vezes identificado como o último autor nos artigos. O questionário continha perguntas objetivas com respostas em múltipla escolha, além de estimular o pesquisador a fazer algum comentário que julgasse necessário. Foram abordados especificamente o critério para interromper a infiltração, a definição de saturação da lesão e para que tipos de lesão a infiltração intralesional seria aplicável.

4.3 Processo de validação

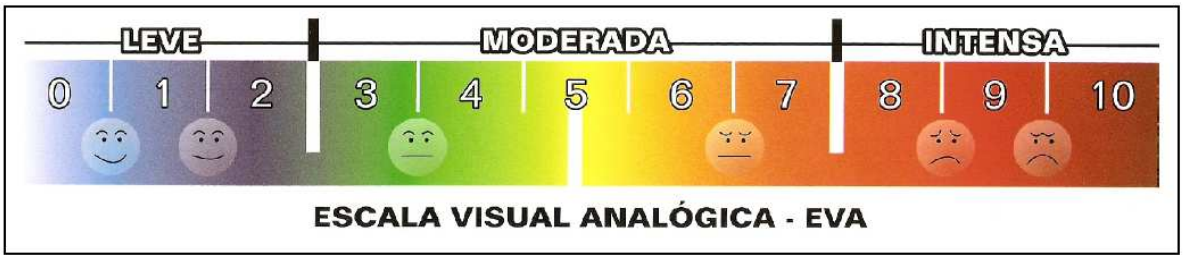
Inclui a validação de conteúdo, critério e construto. A validação de conteúdo foi realizada através da inspeção computadorizada executada em colaboração com profissionais da ciência da computação e detalhada no item 4.3.1. Após implementadas as modificações sugeridas pelo processo de inspeção formal, versão corrigida do POP foi utilizada para orientar a realização da infiltração em estudo clínico de avaliação de eficácia e segurança da terapia intralesional com antimoniato de meglumina. Inicialmente apenas os três profissionais com experiência prévia em infiltração intralesional executavam o procedimento, sempre sob a observação da enfermeira-pesquisadora. Após 6 meses, médicos residentes estagiando no CRL, sem qualquer experiência prévia na técnica, também passaram a executar a infiltração seguindo o roteiro de ações proposto no POP, também sob a observação da pesquisadora. Para guiar a observação da execução dos procedimentos de infiltração, elaborou-se um *check-list* (Figura 2) contendo 10 questões relacionadas às ações recomendadas no POP, preenchido pela enfermeira-pesquisadora.

FIGURA 2 - *Check-list* de observação

	SIM	NÃO
1. **Procedeu a infiltração de lidocaína utilizando uma agulha de insulina:**	( )	( )
2. **Realizou botão anestésico em pele integram (área subjacente à lesão):**	( )	( )
3. **Aspirou completamente o conteúdo da ampola de Glucantime® (5 ml):**	( )	( )
4. **Introduziu a agulha através do botão anestésico**	( )	( )
5. **Introduziu a agulha em direção ao centro da lesão:**	( )	( )
6. **Manteve a inclinação da agulha paralela à base da lesão:**	( )	( )
7. **Manteve o bisel voltado para cima:**	( )	( )
8. **Retrocedeu a agulha em direção à borda enquanto infiltrava suavemente a medicação:**	( )	( )
9. **Demonstrou conhecer saturação como inchaço / edema (com ou sem palidez):**	( )	( )
10. **Respeitou o volume máximo diário de Glucantime® permitido:**	( )	( )

As questões permitiam avaliar se as ações recomendadas no POP eram realizadas, se isto se dava de forma correta ou incorreta, na sequência proposta no POP, de modo a se obter uma pontuação de 0 a 10 que indicava o grau de adesão às instruções. Todas as infiltrações foram observadas pela mesma pesquisadora. Além das questões específicas avaliando adesão, registrava-se a duração do procedimento e uma escala numérico-visual de dor (PRESENTE; 1989) era aplicada ao paciente (Figura 3). Trata-se de uma escala ilustrada consistindo em uma linha horizontal que vai de zero (nenhuma dor) a uma quantidade extrema de dor, definida como 10.

FIGURA 3 - Escala visual analógica (EVA) de dor



Fonte: PRESENTE, 1989.

Para a avaliação do sangramento, utilizou-se a escala adaptada Fromme-Boezaart (BOEZAART, 1995), proposta para avaliação de sangramento em sítio cirúrgico e cuja graduação vai de 0 a 5 (Figura 4). Esta escala originalmente utiliza a frequência de sucção como medida de intensidade de sangramento. Entretanto, como sucção mecânica é um tipo de procedimento não realizado em ambiente ambulatorial, cenário da técnica de infiltração intralesional, "sucção" foi substituída por "limpeza do sangramento através de gaze ou compressas". Por fim, ao término da infiltração, o estado de saturação da lesão era avaliado pela pesquisadora. O alcance do estado de saturação foi estabelecido *a priori* como o resultado final pretendido do procedimento de infiltração intralesional, tal como preconizado de forma unânime na literatura científica. A definição dos critérios necessários para a constatação da condição "saturação" consistiu em uma questão-pergunta deste estudo, a ser apresentada em Resultados.

FIGURA 4 - Escala de sangramento

Grau 0	Nenhum sangramento
Grau 1	Sangramento mínimo, nenhuma intervenção é necessária
Grau 2	Sangramento leve, limpeza do campo com gaze é ocasional
Grau 3	Sangramento moderado de modo a prejudicar a visão da lesão segundos após a limpeza do campo com gaze, que precisa ser frequente
Grau 4	Sangramento moderado a intenso de modo a prejudicar a visão da lesão imediatamente após limpeza do campo com gaze, que precisa ser muito frequente
Grau 5	Sangramento é muito intenso e compromete a visão da lesão mesmo com limpeza contínua do campo com gaze, que precisa ser contínua

Fonte: adaptado de Boezaart et al., (1995)

4.3.1 Inspeção ou validação de conteúdo

Para esta análise, que refere-se ao julgamento da qualidade das instruções contidas no POP ou, em outras palavras, se este abrangia todas as ações necessárias ao procedimento, sem elementos (ou ações) desnecessários, aplicou-se um método computadorizado (por isso chamado formal) de avaliação de conteúdo (RIBEIRO et al., 2014) . Trata-se de ferramenta previamente validada para verificação de documentos de especificação de software (COTA et al*.,* 2017) e desenvolvido por cientistas de informática da Universidade Federal do Rio Grande do Sul, Brasil, pela primeira vez aplicado a um instrumento na área da saúde. O método é baseado em seis etapas.

Etapa 1: pré-processamento do instrutivo original: esta etapa consiste em traduzir a primeira versão do POP para uma notação de computador em que cada ação corresponde a uma instrução (linguagem computadorizada) no procedimento a ser verificado.

Etapa 2: identificação de entidades: consiste em identificar os elementos (entidades) que aparecem no instrutivo. Normalmente, as entidades em um documento são representadas por substantivos ou frases nominais, como "médico", " lidocaína", "seringa", “agulha”.

Etapa 3: identificação de ações: o próximo passo é identificar as ações essenciais a serem realizadas separadamente pelo profissional. As ações geralmente são representadas por verbos e frases verbais e correspondem a operações envolvendo as entidades. O primeiro passo da metodologia torna este passo mais simples, pois pode-se extrair uma ação para cada instrução traduzida.

Etapa 4: caracterização de condições e efeitos como estados. Este é o passo de modelagem, onde o roteiro escrito em linguagem natural (termos médicos) é descrito usando a notação matemática, que é a linguagem computadorizada. Após a extração das entidades e ações apresentadas no instrutivo, as representações gráficas para cada uma delas foram definidas para facilitar a visualização do modelo matemático (Figura 5). Cada parte do gráfico é um elemento de um modelo de Transformação de Gráficos, ou seja, uma estrutura matemática composta de nós e arcos com uma semântica associada que será o alvo de etapas de análise adicionais.

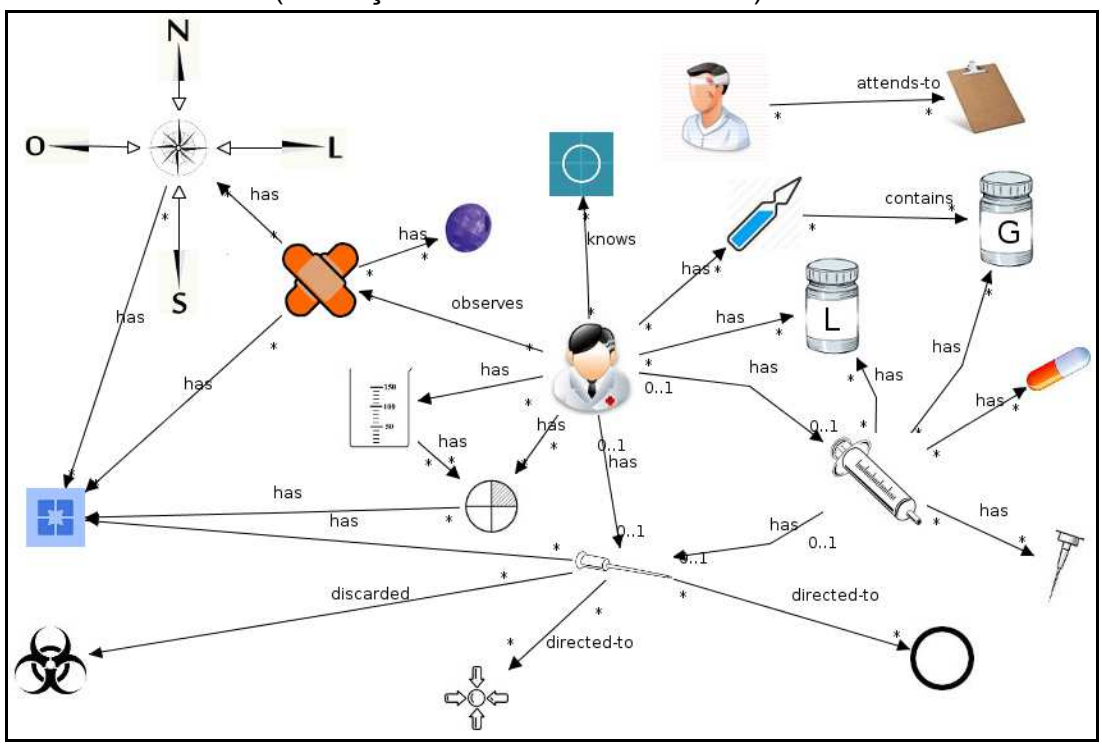
Etapa 5: construção de regras: esta etapa consiste em criar regras de transição para cada ação listada na Etapa 3. Uma regra para uma ação é modelada como uma transição entre dois estados modelados na Etapa 4.

Etapa 6: análise: com todos os passos construídos nas etapas anteriores, várias análises automáticas são realizadas para detectar problemas com o instrutivo.

Assim, resumidamente, o método inclui a transcrição do documento de linguagem natural para a conotação *use case* (UC), uma linguagem para especificar o comportamento esperado do sistema. De acordo com Cockburn (2000) a UC define a relação entre as partes envolvidas em um sistema, descrevendo parte de seu comportamento. Após a transcrição, são identificadas as "entidades" presentes no instrumento, neste caso os objetos ou insumos que serão utilizados, e depois as "ações", os quais são definidos em representação gráfica através de uma modelagem matemática que transforma as condições e os efeitos em "estados" sujeitos a análise. Basicamente a metodologia interpreta os estados de um sistema como gráficos e as mudanças de estado como as regras que transformam estes gráficos.

Assim, cada etapa do procedimento representa um estado, que gera um gráfico correspondente. Ao combinar os gráficos gerados por todas as ações, reunem-se as entidades e relações identificadas no documento original, conforme mostrado na Figura 5. A sequência de gráficos é interligada por regras de transição. Em outras palavras, há um gráfico que representa as pré-condições (ou estado) do sistema antes que uma determinada ação é realizada e um outro gráfico que representa o estado resultante da ação. Com todos esses artefatos construídos nas etapas anteriores, uma série de análises automáticas são realizadas para detectar problemas no instrumento, que são chamadas "questões em aberto" (*open issues*). A inspeção computadorizada envolve três tipos de análises: de conflito, de dependência e de sequência. Os problemas levantados pela inspeção formal, são inconsistências no documento que precisam ser esclarecidas ou modificadas.

FIGURA 5 - Representação gráfica das entidades e ações apresentadas no instrutivo (ilustração do modelo matemático)



4.3.2 Validação de critério

Aspecto da validade relacionado à confiabilidade da própria técnica de infiltração intralesional, enquanto informação capaz de gerar a execução de ação específica, de forma reprodutível. Para realizar esta avaliação, utilizou-se o *check-list* de observação do procedimento de forma a identificar se determinada ação prevista era executada, se era executada de maneira correta, incorreta ou parcialmente correta e se era realizada na sequência recomendada no POP. A estabilidade estatística (robustez) da ferramenta foi estabelecida através da determinação da correlação entre diferentes executores da técnica (comparação entre profissionais de acordo com seu grau de experiência na técnica) e *test-retest* (consistência de pontuação para o mesmo profissional ao longo do tempo), medidas de confiabilidade do instrumento. Os aspectos avaliados foram:

A. precisão do roteiro em levar a execução das ações, avaliado pelo percentual de adesão dos executores às instruções;

B. homogeneidade do processo ou estabilidade estatística, avaliada pela análise na variação para a duração do procedimento, dor referida pelo paciente

(medida pela escala visual-analógica que varia de 0 a 10) e sangramento observado (escala de Boezaart que varia de 0 a 5).

C. confiabilidade intra-executor, avaliado pela variação no grau de adesão ao procedimento pelo mesmo executor comparando seu desempenho em vários procedimentos ao longo do tempo;

D. confiabilidade inter-executor, avaliado pela comparação do desempenho de executores experientes na técnica e profissionais não treinados quanto à adesão ao instrutivo, tolerância pelo paciente, duração e resultado do procedimento.

4.3.3 Validação de construto

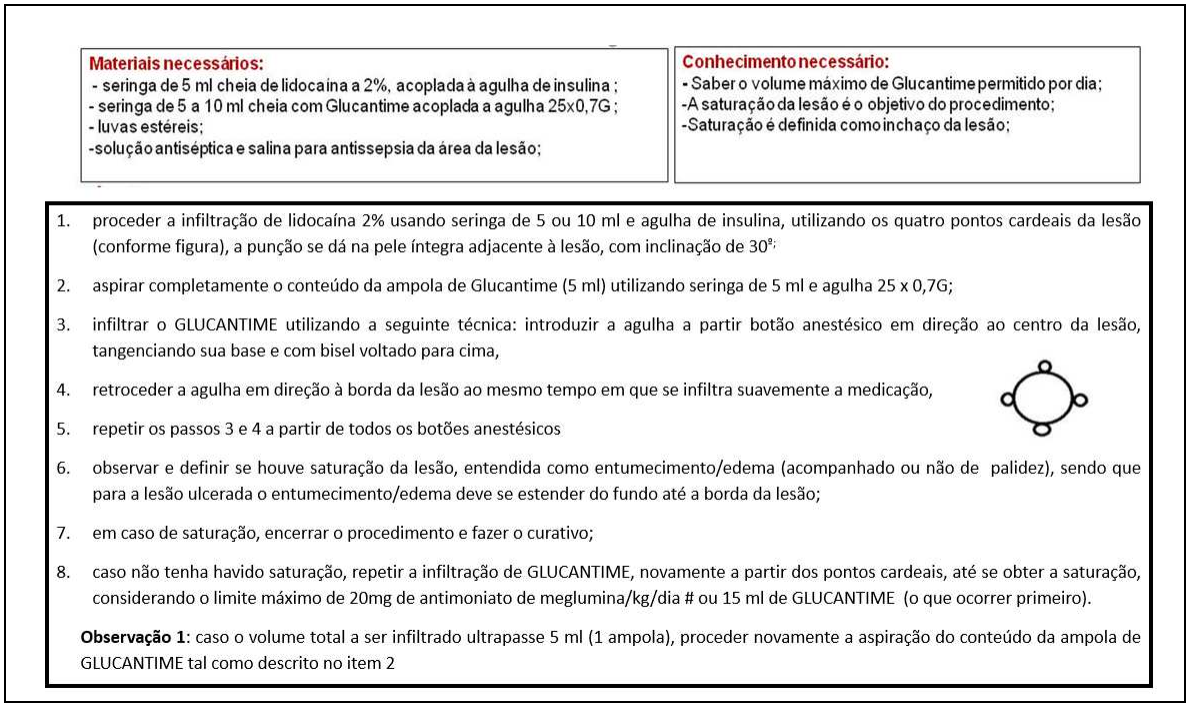
As variáveis escolhidas para a validação de construto, ou seja, para verificar se o resultado obtido está de acordo com as especificações pré-estabelecidas, foram o percentual de alcance de saturação ao fim da infiltração, de acordo com a definição estabelecida pela consulta aos especialistas, e a tolerância dos pacientes ao procedimento, avaliada pela escala visual analógica de dor.

4.4 Análise estatística

Os resultados numéricos que compõem esta análise foram digitados em banco de dados informatizado e analisados com o uso do programa estatístico SPSS® 11.0. A análise descritiva dos dados foi realizada pelas frequências simples das variáveis categóricas, além de médias e medianas, e seus respectivos desvios padrão e intervalo interquartil 25-75% (IQ 25-75%) para as variáveis contínuas, dependendo de sua distribuição. A comparação das médias foi realizada utilizando-se do teste “t” de *Student* e das medianas, o teste de *Kruskal-Wallis*. Para as variáveis categóricas foi utilizado o teste do Qui-quadrado. Para todos os testes, o nível de significância de 5%. A amostra (número de infiltrações a serem observados na avaliação de confiabilidade) foi determinada considerando um nível de confiança de 95% (Z = 1,96) e uma margem de erro máxima de 20% para todos os domínios de interesse. Com base nisso, uma amostra de 24 procedimentos foi estimada para cada grupo para todas as comparações necessárias para a avaliação da estabilidade estatística (profissionais experientes *versus* não experientes, grupo do mesmo profissional ao longo do tempo) e o número mínimo de infiltrações intralesionais solicitadas para a validação do procedimento foi calculado como 72. O

coeficiente de correlação de Spearman e o intervalo de confiança de 95% (IC 95%) para o coeficiente de correlação foram utilizados para comparar a adesão do profissional ao POP de acordo com seu nível de experiência prévia com o procedimento. Um modelo de análise de regressão logística (usando retrocesso passo a passo) para intensidade de sangramento foi construído co-variáveis de ajuste identificadas por análises univariadas com p <0,2.

FIGURA 6 - Versão final do procedimento operacional padrão para infiltração do antimonianto de meglumina



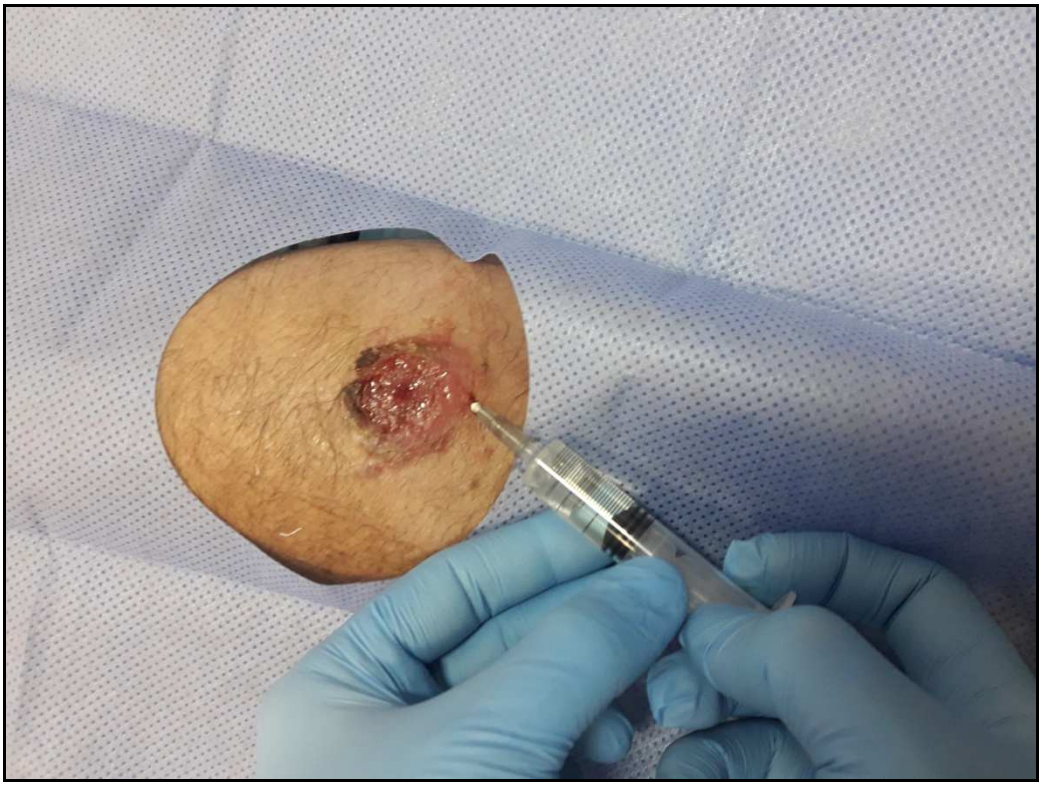
Materiais necessários:
- seringa de 5 ml cheia de lidocaína a 2%, acoplada à agulha de insulina ;
- seringa de 5 a 10 ml cheia com Glucantime acoplada a agulha 25x0,7G ;
- luvas estéreis;
-solução antiséptica e salina para antissepsia da área da lesão;

Conhecimento necessário:
- Saber o volume máximo de Glucantime permitido por dia;
-A saturação da lesão é o objetivo do procedimento;
-Saturação é definida como inchaço da lesão;

1. proceder a infiltração de lidocaína 2% usando seringa de 5 ou 10 ml e agulha de insulina, utilizando os quatro pontos cardeais da lesão (conforme figura), a punção se dá na pele íntegra adjacente à lesão, com inclinação de 30º;
2. aspirar completamente o conteúdo da ampola de Glucantime (5 ml) utilizando seringa de 5 ml e agulha 25 x 0,7G;
3. infiltrar o GLUCANTIME utilizando a seguinte técnica: introduzir a agulha a partir botão anestésico em direção ao centro da lesão, tangenciando sua base e com bisel voltado para cima,
4. retroceder a agulha em direção à borda da lesão ao mesmo tempo em que se infiltra suavemente a medicação,
5. repetir os passos 3 e 4 a partir de todos os botões anestésicos
6. observar e definir se houve saturação da lesão, entendida como entumecimento/edema (acompanhado ou não de palidez), sendo que para a lesão ulcerada o entumecimento/edema deve se estender do fundo até a borda da lesão;
7. em caso de saturação, encerrar o procedimento e fazer o curativo;
8. caso não tenha havido saturação, repetir a infiltração de GLUCANTIME, novamente a partir dos pontos cardeais, até se obter a saturação, considerando o limite máximo de 20mg de antimoniato de meglumina/kg/dia # ou 15 ml de GLUCANTIME (o que ocorrer primeiro).

Observação 1: caso o volume total a ser infiltrado ultrapasse 5 ml (1 ampola), proceder novamente a aspiração do conteúdo da ampola de GLUCANTIME tal como descrito no item 2

FIGURA 7 - Ilustração de procedimento de infiltração intralesional de antimoniato de meglumina



5 RESULTADOS

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Using formal methods for content validation of medical proceduredocuments

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Using formal methods for content validation of medical procedure documents

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ABSTRACT

Objective: We propose the use of a formal approach to support content validation of a standard operating procedure (SOP) for a therapeutic intervention. Such an approach provides a useful tool to identify ambiguities, omissions and inconsistencies, and improves the applicability and efficacy of documents in the health settings.
Materials and methods: We apply and evaluate a methodology originally proposed for the verification of software specification documents to a specific SOP. The verification methodology uses the graph formalism to model the document. Semi-automatic analysis identifies possible problems in the model and in the original document. The verification is an iterative process that identifies possible faults in the original text that should be revised by its authors and/or specialists.
Results: The proposed method was able to identify 23 possible issues in the original document (ambiguities, omissions, redundant information, and inaccuracies, among others). The formal verification process aided the specialists to consider a wider range of usage scenarios and to identify which instructions form the kernel of the proposed SOP and which ones represent additional or required knowledge that are mandatory for the correct application of the medical document.
Conclusion: By using the proposed verification process, a simpler and yet more complete SOP could be produced. As consequence, during the validation process the experts received a more mature document and could focus on the technical aspects of the procedure itself.

1. Introduction

A standard operating procedure (SOP) is a common tool used in clinical settings to enable uniformity of procedures that are (or will be) performed by different stakeholders in different scenarios. SOPs are also crucial in a research protocol to ensure that all data collected meet minimum requirements, thus allowing further comparative analysis. Following the same principle and on a larger scale, clinical guidelines are a growing requirement in the health area, for harmonize both diagnostic and therapeutic activities. Thus, the development and validation of models applicable to human processes are highly desirable.

Adherence to standard procedures is crucial and can be affected by many attributes of the document, including its precision and clarity [1]. A SOP written in natural language is prone to problems such as omissions, ambiguities, and wrong information, among others, that may negatively affect its application. This work proposes a new approach to improve the correctness, completeness, and accuracy of the statements describing a standard medical procedure, thus improving the quality and the reliability of such documents.

In the medical community, one is mostly concerned with the validation of technical documents, such as clinical guidelines and SOPs, which means, in that context, how correct and useful is the proposed standard, as well as the level of adherence to these recommendations [1–3]. The verification of the document itself (the readability and clarity of the text describing the standard procedure) is considered in the validation process, but there is no systematized method to find possible faults (other than the technical or content-specific ones) in the document itself. Up until now, this aspect of the instrument validation has been done by experts on the subject being standardized, with the main goal of assessing whether the SOP reflects the best practice. For example, the experts discuss and agree upon what will be considered as a successful result of the procedure. We intend to show that this manual revision, although essential from the technical

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point of view, can still miss important flaws in the SOP structure and text. As a result, one can have a less effective procedure, although technically accurate, due to problems in the structure of the document.

Some authors argue that automation could improve adherence levels [4] and there are several examples of applying computerized guidelines [5–8]. Several approaches and languages also have been proposed to represent and disseminate various types of clinical guidelines [9]. Such approaches rely on the use of formal languages (defined by strict syntax and semantic rules) to reduce the problems related to ambiguity. Furthermore, associated computer tools are used to execute the guideline in the context of decision support systems [9]. Computer-interpretable clinical guidelines can be considered in environments where electronic health systems are available not only to register patient data, but also to support decision making. However, this is still not a reality in many regions of the world, mainly in poor and developing countries. Those regions, on the other hand, are the ones that can mostly benefit from SOPs, since their medical staff is normally overwhelmed and working with minimal material support. Therefore, SOP documents written in natural language are still a necessity. To be effective, such documents must be not only technically accurate, but also clear and simple to follow.

In this paper, we propose the use of a formal method during the content validation phase of a SOP for the treatment of cutaneous leishmaniasis (CL). The proposed approach is based on a theoretical model previously described in [10] for the verification of software specification artefacts. Our proposal consists thus of a two-step content validation process: first, the medical document produced in natural language is analyzed with respect to its structure using a formal computer-aided method, and after that, the verified document can be validated by medical experts, in relation to its technical aspects. Our results show that the formal verification of a given document can pinpoint a number of issues that are not normally perceived by reviewers as possible problems. Without the formal verification, those issues can remain unknown, and compromise the accurate evaluation and applicability of this type of health tool.

The paper is organized as follows: Section 2 discusses some useful approaches applicable in the identification of possible problems present in documents written in natural language. Section 3 describes the development of a medical SOP, presented as case study in this paper. Section 4 reviews the formal verification methodology used in this work and Section 5 details the verification process applied to the CL treatment SOP. The results of the verification process are presented and discussed in Section 6. Section 7 concludes the paper and presents known limitations and possible future work.

2. Related work and theoretical framework

2.1. Validation of Health instruments

In order to fulfill their function of guaranteeing effectiveness and uniformity of performance, the SOPs must undergo a careful validation process. The assessment of reliability includes the following aspects: (i) the internal consistency of the SOP (content validation); (ii) its stability to changes in critical conditions (criterion validation); and (iii) the measurement of the extent to which the set of instructions leads to the intended result (construct validation).

Criterion validity indicates the degree to which changes in process/performer influence the outcome. It is also called statistical stability and was established by determining the inter-rater (agreement between the professionals) and test–retest (consistency of scoring over time) reliabilities.

Construct validity refers to the demonstration that the instrument actually does what it intends to do. For example, in the case of a therapeutic intervention, this might mean a minimum cure rate. The evidence required for such validation is obtained through a series of statistical tests to interrelate theoretical constructs about the relationship between the variables to be measured.

Content validity, the focus of this work, refers to the judgment on the quality of the instrument description, i.e., whether it actually covers all actions included in the proposed procedure and whether it contains elements (or actions) that can be assigned to other procedures. Content validity typically results from the perusal of different expert examiners, who review the representativeness of the items in relation to areas of content and relevance of the objectives to be reached. As detailed in Section 3 for the SOP used in this work, this aspect is the first one to be addressed when a new SOP is proposed. Once this first stage of quality assessment is complete, the criterion and construct validation can be performed. In this paper, we focus on this first step of the validation process (the content validation) and aim to demonstrate that the current informal approach used to perform this step can benefit from the use of formal methods.

2.2. Verification of artefacts written in natural language

Software requirements and specification documents are also written in natural language, and studies have shown that most software faults have their origin in errors present in these artefacts [11]. The manual inspection or revision of software artefacts (requirements, specification and design documents or source code) has been well documented in the literature [12,13].

Fagan [14] proposed the first software inspection method and many approaches followed [15], aiming at improving the method effectiveness in finding errors. A proper inspection process is considered a "formal revision" approach, as it requires preparation, definition of roles among reviewers, standard checklists, and follow up procedures [16]. Software inspection has been shown to be an effective but costly and time-consuming strategy [17]. Informal revisions such as peer revision, on the other hand, are simpler and cheaper, but less effective [18].

Many studies have shown that the efficacy of an inspection or revision process ultimately depends on the reviewers training and experience not only in the domain, but also in the revision process [16,19,20,21]. An inspection process that uses inexperienced reviewers (even if they are experts in the domain) is more likely to deliver an artefact with important problems of omissions and ambiguities. Verification checklists try to tackle such problems in the revision process. However, a checklist prepared by the same author of the procedure under verification can be biased, which can reduce its efficacy. Finally, revision meetings without proper preparation risk to be unfocused and therefore less effective. When problems in the document remain undetected, they might incur additional cost and re-work.

In the case of clinical guidelines and SOPs, the revision usually performed in the content validation phase can be considered as an informal revision technique. Reviewers work independently and are commonly guided by a form with specific evaluation points [22,23]. When a problem in the procedure description is detected only in the later validation phases (criterion and construct validation), it may compromise the reliability of previously collected results and require the definition of a new validation round. If the problem remains undetected until the standard dissemination phase, the adherence to the SOP and the effectiveness of the proposed procedure may be reduced or even compromised.

Despite the problems of the informal revision, the implementation of a proper "*formal inspection*" approach is unrealistic in the medical domain as it requires specific training of each possible reviewer. On the other hand, the *formal verification* of an artefact written in natural language has been explored before and can be performed automatically using a computer-aided approach [24–26].

SOPs are very similar in format to a software specification, although targeted to humans. Both are written in natural language and intend to document a set of actions that must be executed or answered, i.e., that must generate a result or reaction. Both artefacts assume that a certain

INTRALESIONAL INFILTRATION TECHNIQUE (VERSION 1.0)

- ✓ Wash the wound with sterile saline solution 0.9% and antiseptic solution;
- ✓ Put sterile gloves on
- ✓ Dry for apposition with sterile gauze; set up sterile field
- ✓ Check the crusts and / or devitalized tissue on the surface of the lesion. If present, performs mechanical debridement until the bottom of the lesion becomes visible (in case of ulcerated lesions);

==========

PROCEDURE:

1. Use a 5ml or 10ml syringe with a 25 G x 0.7 needle to aspire 2% Lidocaine. Proceed with the infiltration of 2% lidocaine using an insulin needle, through the four cardinal points around the lesion (see figure), until 4 anesthetic buttons of approximately 3 x 3 mm^2 each have been formed.

2. Completely aspirate the contents of the Glucantime ampoule (5ml) using a 5 ml syringe and 25 x 0.7g needle.
3. Discard the needle used for medication intake.
4. Couple another needle (25 x 0.7G in case of lesions larger than 1cm and insulin needle in case of minor injuries).
5. Infiltrate Glucantime using the following technique: insert the needle from anesthetic button toward the center of the lesion, tangential to its base and bevel facing upward.
6. Move the needle back toward the edge of the lesion while gently infiltrating the medication. The total infiltrated volume should be divided into 4 equal parts so that 4 applications in the 4 cardinal points can be performed.
7. Observe and determine whether there is saturation of the injury, seen as swelling / edema (with or without paleness). In case of ulcerated lesions, swelling / edema should extend from the bottom to the edge of the lesion.
8. In case of saturation, end the procedure and bandage the area; if there is no saturation, repeat Glucantime infiltration using 1 ml at a time. Infiltration is performed from the cardinal points until saturation is obtained or until the maximum limit of 20 mg of meglumine antimoniate / kg / day # or 15ml Glucantime is achieved (whichever happens first).

==========

 # OBSERVATION 1: if the total amount of Glucantime to be infiltrated exceeds 5 ml (1 ampoule), proceed again the aspiration of Glucantime ampoule as described in Step 2;.

 # OBSERVATION 2: each ml of Glucantime contains 81 mg of antimony meglumine, the maximum volume in ml of an individual is obtained as follows: (weight (kg) x 20) / 81 (max 15 ml).

 # OBSERVATION 3: this amount refers to the maximum volume that can be applied in an individual, including all lesions, in one day.

Fig. 1. Original document of cutaneous leishmaniasis treatment SOP.

system (computer or human) is the target of the described instructions. The target system, in its turn, can be represented as being in a certain state, which changes upon the execution of an action or instruction described in the document. Furthermore, SOPs can be used as the main reference for the development of software systems that support their application. Therefore, its clarity and correction are mandatory. Hence, we propose to apply a formal verification methodology to a medical SOP. Such methodology has been previously presented for the verification of software specifications. We further show that this approach can improve the content validation phase of this health instrument. We assume the verified SOP document will be used (executed) by medical staff that is unfamiliar with formal languages. Thus, although we build a formal model of the SOP to perform the analyses, we keep the informal description (document written in natural language) as the main artefact to be used during the dissemination of the SOP. Hence, improvements pointed out by the formal analyses are applied not only to the model, but to the informal description as well.

3. An overview of the case study: SOP for cutaneous leishmaniasis treatment

Leishmaniasis is a neglected and highly prevalent disease in poor regions of the world. One of the main problems in the CL management is the high toxicity related to the systemic treatment that is currently available and based on antimony derivatives. Thus, topical and less toxic therapies for the disease are being actively studied. However, there is a lack of standardization procedures for this alternative therapy which precludes its dissemination and cost-effectiveness analysis, among other problems.

René Rachou Research Center (Fiocruz-MG) is currently developing a SOP for a specific procedure for the treatment of cutaneous leishmaniasis, namely: pentavalent antimony (Glucantime®) intralesional infiltration. The intralesional infiltration is considered a medical procedure, and therefore an action encompassing both understanding and knowledge. Once validated, this medical procedure will be disseminated in regions with scarce infrastructure and with medical staff working in stringent conditions. Therefore, documents written in natural language must be used and the simplicity and clarity of those

documents are essential requirements

The treatment SOP developed by Fiocruz-MG precisely targets the possible and undesirable variability in the alternative therapeutic intervention. Hence, each step must be clearly and unambiguously defined, so that it can be used as a simple reference by any physician. To validate the procedure's guidance we chose to apply the psychometric principles [27,28] associated with automated methods of software verification, as described next.

Besides content validation, this SOP is also under the process of construct and criterion validation. Another step of utmost importance is the cost-effectiveness analysis of this new cutaneous leishmaniasis therapeutic approach. This analysis also depends on the standardization of the intervention to ensure the reliability of the collected data.

The intralesional infiltration SOP was developed following a comprehensive and progressive process that started with the construction of the instrument and a first (informal) content validation campaign. As the first step, we performed a systematic search of all descriptions of the procedure available in trial register bases and medical databases such as MEDLINE and LILACS. A total of 21 studies were identified and analyzed with respect to the description of the intralesional procedure. More specifically, we looked for the following information: use of anesthesia; needle gauge specification, angulation, direction and depth during the infiltration; volume of medication infiltrated or any other criteria used to stop the infiltration. To complete this analysis, our second step aimed at identifying all the stages comprising the intralesional infiltration process. This was done through observation of the actual procedure performed by an experienced professional in a CL Referral Center. After gathering and sorting all this theoretical and practical information about the infiltration procedure, we observed many conflicting and/or unresolved questions in the set of instructions. Hence, we identified in the literature a panel of expert investigators with wide experience in the infiltration technique. The third step of the SOP construction consisted thus of submitting all unresolved or conflicting issues about the procedure to the panel of experts. The experts were contacted electronically and invited to answer a several rounds multiple-choice questionnaire (Delphi methodology [29]). The questionnaire also included a field for the investigators to include any additional comments they saw necessary. Based on the received answers, a first document was created.

The original SOP is a document composed of 4 preparation steps, 9 steps that define the medical procedure and 3 final observations that may affect the intervention (Fig. 1). Each step of the original procedure contains several instructions and information to be considered. According to the definition established by experts in the treatment, the final result (product) to be achieved after the procedure is a lesion state defined as saturation, which means the presence of swelling of the entire base of the lesion, represented by visible edema and/or pallor.

Despite following a defined methodology, one can observe that content validation is still an informal process, where decisions leading to conflicting actions are taken based on aspects intuitively identified by observers, based on their previous knowledge and individual experience with the subject in question. Furthermore, we note the lack of a specific verification step regarding the readability, clarity, expressiveness and other structural quality criteria of the SOP. The revision performed by experts (as described above) focuses on the procedure itself, aiming at finding a consensus on the technical aspects of the proposed instrument. Problems in the structure of the document are more likely to be raised when they clearly affect its correctness. On the other hand, problems related to ambiguity or omission of information (considered as tacit knowledge) have no guarantee of being detected.

Thus, we have included the formal verification of the document as an additional step (the fourth one) of the content validation process, as described in the sequel of this paper.

During the formal verification process of the SOP, the medical team made several modifications in the document to answer and solve the issues raised by the formal analysis. For criterion and construct validation, medical professionals with and without prior experience with intralesional approach performed 118 intralesional infiltration procedures following the SOP and under the supervision of a same observer, in a subsequent clinical validation study. The influence of critical conditions' changes (compliance with the guidance's instructions and professional experience) on outcome conformity (saturation status achievement), tolerability (scale of pain referred) and safety (bleeding) were assessed.

4. Formal verification methodology

Junior et al. [10] propose a formalization and verification approach for software specification artefacts written in natural language using the Use Case (UC) notation.

Use Cases are a popular model to specify system behavior, and are an important artefact for system design and evolution. According to Cockburn [30], a UC defines a contract between stakeholders of a system, describing part of its behavior. The main purpose of a UC description is the documentation of the expected system behavior thus easing the communication between stakeholders (often including non-technical people), about required system functionalities. For this reason, the most usual UC description is the textual form.

A general format of a UC contains a unique name, a primary actor (trigger of the UC), a primary goal and a set of sequential steps modeling the successful interaction between the primary actor and the system toward the primary goal. A sequence of alternative steps is often included to represent exception flows. Pre- and post-conditions are also listed to indicate, respectively, conditions that must hold before and after the UC execution.

To be able to apply formal verification techniques over the textual artefact, the first step is to obtain a formal version of the UC, that is, a mathematical model of the UC has to be built. Since the UC describes a process (a series of actions that should be followed to accomplish some task), the model must have some means to describe *states* (representing the initial, intermediate, and final situations reached by the process) as well as *changes of state* (representing the behavior of each step of the UC). Note that each UC describes a process of some domain or knowledge, and therefore the *vocabulary* of this domain should be incorporated in the formal model in some way.

The UC verification approach detailed in [10] is based on graph transformation (GT) formalism. Graphs are mathematical structures composed of nodes and arrows (connecting the nodes). In the following we explain how UC vocabulary, states and state changes are represented in this formalism:

Vocabulary – Type graph: Names of entities that appear in the UC are represented as nodes and relationships between them as arrows. This way, we obtain a graph that is called type graph, because it depicts the types of elements that may be part of states. For instance, in the medical document, *syringe* and *needle* will be nodes connected by a *has* arrow, indicating that it is possible that in some state a syringe has a needle;

States – Graphs: Each state of a process may contain zero or more elements of each type. For example, a state may contain two syringes and no needles, or one syringe with a needle, or one syringe with a needle and a second syringe with no needle, etc.;

State changes – Rules: Rules represent actions. A rule consists of two graphs, called left-hand side and right-hand side, representing, respectively, the situation (pre-condition state) in which the action may occur and the effect (resulting state) of the action. For example, a rule representing the action of attaching a needle to a syringe may have as left-hand side a syringe and a needle with no connection between them, and have these elements connected by a *has* arrow in the right-hand side. Typically, one obtains one rule for each step of the UC, which means that it is quite easy to relate the generated formal model to the original document. Notice that this formalism does not model temporal ordering of the rules. Indeed, any rule can be applied at any time provided that all of its pre-conditions hold. In other words, whenever

"*Use a 5ml or 10ml syringe with a 25G x 0.7* mm *needle to aspirate 2% Lidocaine. Proceed with the infiltration of 2% Lidocaine using an insulin needle, through the four cardinal points around the lesion (see figure), until 4 anesthetic buttons of approximately 3 x 3 mm² each have been formed.*"

we generate the following steps in the corresponding UC:

1	MD aspirate 2% Lidocaine using 5ml or 10ml syringe and a 25G x 0.7mm needle
2	MD performs 2% Lidocaine infiltration using an insulin needle, through the four cardinal points around the lesion (see figure) until 4 anesthetic buttons of approximately 3 x 3 mm^2 each have been formed.

Fig. 2. Two initial steps of the SOP for cutaneous leishmaniasis treatment.

the state of the system matches the left-hand side of a rule, this action occurs and the right-hand side of the rule defines the new state of the system.

By analyzing the properties of the GT model corresponding to an UC one can detect inconsistencies in the UC description. In this work we adapt the method proposed in [10] to formally verify a medical SOP. The verification methodology is divided into seven steps as described below. Section 5 details the execution of each Step described below to an extract of the medical document. Then, a summary of the overall verification is presented in Section 6. The steps of the verification methodology are:

Step 0 – Pre-processing: This pre-processing step transforms the original medical document (free textual form) to a UC notation. This translation keeps the instructions in natural language (using the same words and actions present in the original document), but splits an instruction with multiple actions into multiple instructions, reducing the size and complexity of each one. Thus, each action described in the SOP corresponds to one instruction in the UC notation. This step is not mandatory since the definition of the GT model is a manual process and one can infer the actions and states from an unformatted textual description. We note however that models at different levels of abstraction can be defined from the same specification and different issues are raised according to the model. Hence, the translation of the textual description to a formatted UC notation helps the designer to focus on the actions and states that need to be modeled. This leads to a simpler and less abstract GT model, thus improving the effectiveness of the verification process (which is based on this notation).

Step 1 – Identification of entities and relationships: This step consists in identifying the entities that appear in the SOP. Usually the entities in a document are represented by nouns or noun phrases. After identifying the entities and relationships between them, a graphical element and a unique name are chosen to depict each entity and arrows depict each relationship, giving raise to the type graph of the GT model.

Step 2 – Identification of actions: The next step is to identify the essential actions to be performed. Actions are usually represented by the verbs and verb phrases and correspond to operations involving the entities. The pre-processing step (translation of the SOP to the UC notation) makes this step simpler as one can extract one action for each translated instruction. Typically, there will be one action for each UC step. The result of this step is a list of actions together with their pre- and post-conditions, where the pre-conditions describe the situation in which the action should be performed and the post-conditions describe the effect of the action.

Step 3 – Graphical visualization of conditions and effects: Now we examine each condition and effect appearing in the list created in the last step and assign graphical representations to them using the graphical elements defined in Step 1.

Step 4 – Primary Verifications phase: Basic manual verifications are performed regarding the consistency of the extracted information. We look for inconsistencies that might affect or even prevent the construction of the GT model, such as entities or conditions that are mentioned but never used, actions or effects of an action that are not clearly defined, and so on. For example, one may identify that insulin needle is listed as required material but never used in the procedure. As another example, one may identify at this point that the concept of saturation is not clearly defined (hence cannot be represented accordingly).

Name	Intralesional Infiltration Technique (Original)
Preconditions	- Patient meets treatment criteria - Lesion area is known
Postconditions	- Patient under medication
Primary Actor(s)	Physician (MD)

Step	**Main Scenario Actions**
1	MD aspires 2% lidocaine using 5ml or 10ml syringe and a 25G x 0.7 mm needle
2	MD performs 2% lidocaine infiltration using an insulin needle, through the four cardinal points around the lesion (see figure) until 4 anesthetic buttons of approximately 3 x 3 mm2 each have been formed.
3	MD aspirates the contents from Glucantime ampoule (5 ml) using 5ml syringe and 25G x 0.7 mm needle
4	MD discards the needle used for the aspiration of the medication
5	MD couples another 25G x 0.7 mm needle in the syringe with the medication
6	MD inserts the needle from an anesthetic button towards the center of the lesion, tangential to its base with the bevel facing up
7	MD retracts the needle towards the border of the lesion and at the same time injects 1/4 of the estimated volume of medication.
8	MD repeats steps 6 and 7 in the remaining anesthetic buttons.
9	MD observes that lesion is saturated (edema has formed)
10	MD ends the procedure.
Step	**Alternative Actions**
3a1	MD aspirates the contents from Glucantime ampoule (5 ml) using 10ml syringe and 25G x 0.7 mm needle
3a2	Continue on Step 4 of the Main Scenario
9a1	MD observes that lesion is not saturated
9a2	MD injects, from the closest anesthetic button, 1ml of Glucantime at each non-saturated region of the lesion
9a3	Continue from Step 9 of the Main Scenarion
Step	**Exception Actions**
9b1	The total injected volume of Glucantime is higher than the maximum allowed (15ml)
9b2	MD ends the procedure

Fig. 3. SOP for cutaneous leishmaniasis treatment using Use Case notation.

Inconsistencies detected at this point can indicate a problem either in the UC or in the modeling. In either case, an open issue is raised and must be solved before continuing the modeling process (by rewriting the UC and/or the model). Alternatively, the analyst can make assumptions and annotate the problem as an open issue to be resolved/confirmed later on. This step is similar to an inspection, but the reviewer in this case focuses on the verification of very few aspects of the document.

Step 5 – Construction of rules: When all basic inconsistencies detected in Step 4 are solved, the graph transformation model can be completed by the construction of rules. For each action (Step 2) we build a rule using the graphical representations defined in Step 3. The left-hand side of the rule is a graph containing the elements corresponding to the conditions of the action and the right-hand side is a graph containing the effects of the action. According to the semantics of the GT formalism, any element that appears in the left-hand side and not in the right-hand side of a rule is deleted by the rule, whereas elements that appear only at the right-hand side (and not in the left) are created by the rule. Any item that is both in the left- and right-hand side is

Table 1
Entities identified in the Use Case and their corresponding (chosen) graphical representation.

Patient		Insulin needle	
Lesion		Anesthetic buttons	
Criteria (for attending the treatment)		5 ml ampoule of Glucantime	
Estimated volume of medicine		Glucantime	
Doctor		25G × 0.7 mm needle	
¼ of estimated volume of medicine		Center of injury	
2% lidocaine		Swelling/edema	
5 ml (or 10 ml) Syringe		Edge of injury	
Cardinal point(s) of Injury		Hospitalar garbage	
Area of the lesion			

preserved. When an entity is deleted in a rule, this means it no longer exists in the system (analogously to an object that is deleted from memory in a computer program) and cannot be referenced afterwards. When relationships are deleted, it means they do not hold anymore. For both, entities and relationships, the creation means that they did not exist at all prior to this point and are created by the rule. This concept is important for the analysis step and will be used in Section 5.

Step 6 – UC analysis: With all those artefacts built on the previous steps, we perform a series of automatic analyses to detect problems in the SOP. The analyses can raise Open Issues (OIs) regarding either some aspect of the document or the modeling. An Open Issue is any inconsistency (e.g., an unexpected dependency or conflict between two rules) raised during the analysis and it indicates a possible problem in the document or in the model. In the first case we have an indication of where to improve the SOP text. Otherwise, we have an indication to change the model of the script. By analyzing all issues raised during the overall verification process one has the opportunity to review and improve the description of the intended behavior. Currently, three kinds of analyses are performed: Conflict analysis, Dependency analysis and Rule sequence.

Conflict analysis tells us which actions in the SOP are mutually exclusive, that is, it pinpoints decision points, where conditions and/or responses to the actions must be checked. One expects a conflict between rules that represent the outcomes of a selection point. The conflict should exist because there is one rule for each possible outcome and all of them require the same condition graph (left-hand side of the rule). Thus, any of these rules that delete one or more elements of the left-hand side graph precludes the execution of all other rules, thus representing the selection command. On the other hand, one does not expect a conflict between rules that act over distinct elements of the type graph. By running this analysis one is forced to check whether all possible alternatives/scenarios of the medical procedure are described or can be achieved somehow by following the script. One can also check whether each action (rule) manipulates the correct resources.

Dependency analysis identifies relationships between rules. It is used to check whether the dependencies that are expected to occur are actually present in the model. For instance, one expects that 2% Lidocaine is injected in the infiltration points before the medication can be administered. This is a pre-condition to the action that indicates the administration of the medicine and one can expect a dependence indication between these two steps of the document. If this indication does not appear during the analysis, it means the script did not enforce this pre-condition. On the other hand, if an unexpected dependency between rules is detected, it may indicate that either a required pre-condition was omitted or that a super specification of a certain step occurred in the SOP. Such OIs may also indicate some error in the model itself. Modeling errors are usually caused by wrong interpretations of the UC, thus serving as another indicator of revision points in the document. All issues must lead to the careful revision of the SOP text and structure.

Rule sequence is a set of rules that represents the order of execution of all steps of the SOP. Based on the rule sequence, a single rule describing the effect of the whole procedure in one step can be built. This rule exposes, thus, the actual pre-conditions and effects of the medical SOP application. Comparing these calculated pre-conditions and effects with the desired ones it is possible to detect problems like missing requirements/effects. In case alternative scenarios are described in the document, many rule sequences must be constructed and analyzed (one for each scenario).

5. Formal verification of the leishmaniasis treatment SOP

In this section we describe the application of each Step of the verification methodology to an extract of the medical SOP. Although each Step applies to the complete document, we present here only enough information to follow the procedure. Section 6 presents the results of the verification for the whole document.

Step 0 – Preprocessing: To apply the formal verification methodology to the cutaneous leishmaniasis treatment SOP we first need to translate the original document to a UC notation. For example, from the original SOP instruction:

Fig. 3 shows the UC derived from the original SOP after this preprocessing step. Hereafter we refer to this UC as the original repre-

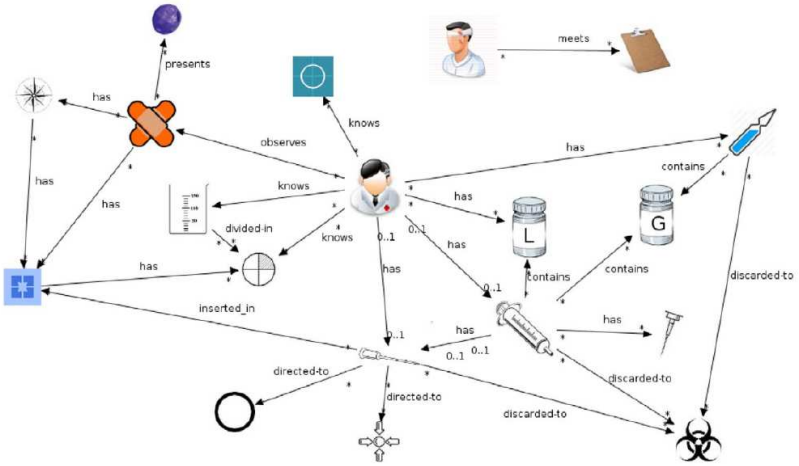


Fig. 4. Type graph representing the entities and relationships involved in the medical procedure.

Table 2
Actions identified in the Use Case together with their conditions and effects.

Action	Conditions	Effects
Aspirates lidocaine	(a) MD has 2% Lidocaine (b) MD has 5 ml (or 10 ml) syringe (c) Syringe has a 25G × 0.7mm needle	(d) Syringe contains 2% Lidocaine
Infiltrates lidocaine	(b) MD has 5 ml (or 10 ml) syringe (d) Syringe contains 2% Lidocaine (e) Syringe has an insulin needle (f) Lesion has four cardinal points	(g) Injury has four anesthetic buttons

sentation of the SOP under verification.

Step 1 – Identification of entities and relationships: In this step, the entities that exist in the UC are identified. For instance: *Medical doctor, 2% Lidocaine, syringe, insulin needle,* 25G × 0.7 mm *needle, lesion, cardinal points*, and *anesthetic buttons* are some of the entities that can be identified in the translated instructions presented in Fig. 2. Then, for each entity, the modeler chooses a corresponding graphical representation that will be used in the type graph. Table 1 shows the graphical representations chosen for each of the entities found in the SOP for CL treatment. We note that in the modeling tool used in this work the same graphic can be used to represent two distinct entities as long as they have unique names. However, the use of distinct graphics improves the graph readability.

Finally, the modeler must identify the possible relationships between these elements. For instance: the syringe may *have* a needle, the medical doctor may *observe* the injury, the patient *meets* the treatment criteria, the ampoule may *contain* Glucantime, among others. These relationships are represented as arrows connecting the graphical representations of the entities. As a result of this Step, one has the type graph depicted in Fig. 4. When numbers appear in a relationship, they indicate a restriction in the number of instances of each entity that can participate in that relationship at a given moment. For example, a syringe can be coupled to at most one 25G × 0.7 mm needle at a time (indicated by the range 0.1 in their relationship). On the other hand, multiple syringes can be connected to the garbage at any time (indicated by the symbol * in the relationship between syringe and garbage).

In case of complex scenarios public databases, such as SNOMED or the UMLS database [31], and ontologies [32,33] can be useful sources of information. They can help in the selection of the most appropriate terminology and in the hierarchical organization of the SOP.

Step 2 – Identification of actions: In this step, the modeler identifies the actions in the UC as well as their conditions and effects, building a table with this information. As an example, Table 2 shows the conditions and effects of the actions defined in Fig. 2.

At the end of this step, one has a table identifying all actions described in the UC. For each action, the table also shows the conditions that must hold for that action to be performed and the effects of that action.

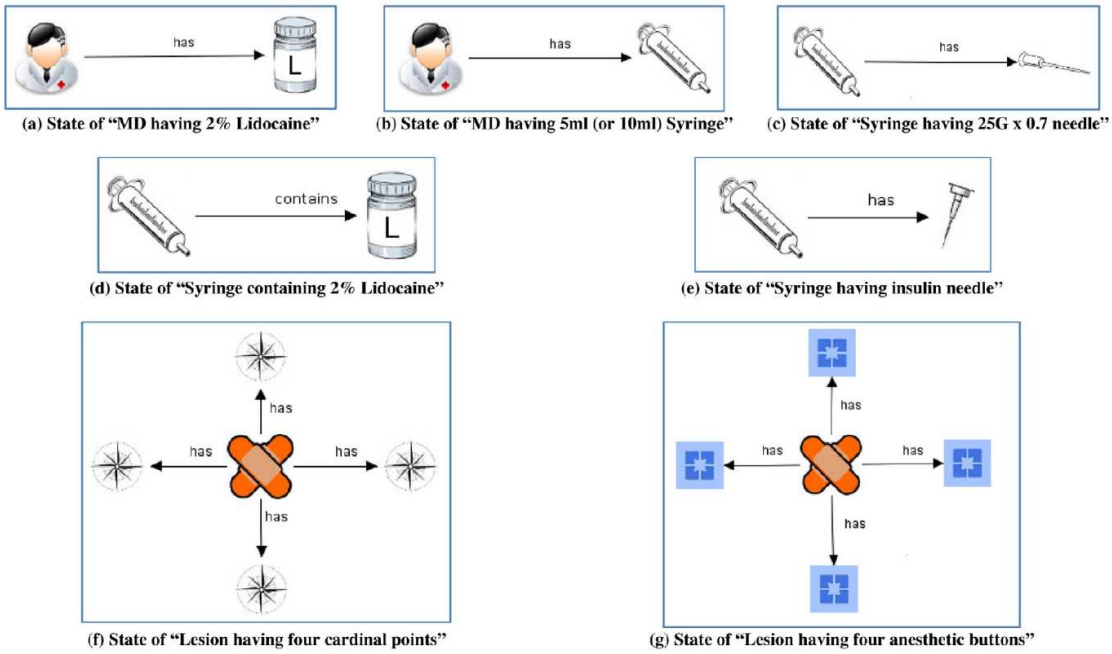
Notice that some effects of an action may be conditions for another one. For instance, in Table 2, the effect of the lidocaine aspiration (*syringe contains 2% Lidocaine*) is a condition for the action of lidocaine infiltration. Furthermore, different actions may share some conditions. In the example, the condition *MD has 5 ml (or 10 ml) syringe* must hold for both actions.

Step 3: Graphical visualization of conditions and effects: The conditions and effects of actions identified in the previous steps represent states the system might be in during the execution of the Use Case. Then, in this step, the modeler builds graphical representations for those states (condition or effect), as shown in Fig. 5. The modeled states must respect the restrictions present in the type graph. This means that only states whose entities and relationships can be mapped to the type graph will be considered valid. This verification is performed in the next step.

Step 4 – Primary Verifications phase: Having all entities, relationships, actions, conditions and effects identified and represented as graphs, one can perform basic manual verifications to ensure that a proper GT model can be defined. Four main questions must be answered at this step:

1. Are all entities listed in Step 1 used (as actor or involved) in some action?
2. Are all branching conditions used in some action?
3. Are the effects of all actions clearly defined?
4. Are all modeled states (conditions/effects) compatible to the restrictions of the type graph?

In our running example, this verification indicated that entities *Medication* and *Glucantime* were not used consistently. In fact, the word



(a) State of "MD having 2% Lidocaine" (b) State of "MD having 5ml (or 10ml) Syringe" (c) State of "Syringe having 25G x 0.7 needle"

(d) State of "Syringe containing 2% Lidocaine" (e) State of "Syringe having insulin needle"

(f) State of "Lesion having four cardinal points" (g) State of "Lesion having four anesthetic buttons"

Fig. 5. Graphs representing states of the medical procedure.

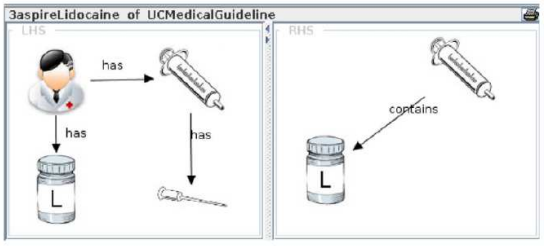


Fig. 6. Rule corresponding to the *aspirate lidocaine* action.

Glucantime is not used after it is aspirated into the syringe (Step 3 of the Use Case). On the other hand, *Medication* did not appear until Step 4. Thus, an issue of possible ambiguity was raised and solved by choosing only one name for that entity. Again, in this step the analyst may refer to standard vocabulary to solve this type of issue. As another example, consider the state of Fig. 5(e). If the type graph of Fig. 4 did not present the *has* relationship between entities *injury* and *Cardinal points of injury*, one would have a modeling problem.

Step 5: Construction of rules: Using the table of actions (Table 2) together with the graphical representations of the states (Fig. 4) generated in previous steps, the modeler proceeds to the construction of the GT model. In this step, one typically generates one rule in the GT formalism for each action identified in the UC. To accomplish that, the analyst combines *(glues)* all state graphs that represent the conditions for an action in the left-hand side of the rule. This combined graph represents the overall pattern that needs to be found in order to apply the rule. Then, he/she combines, in the right-hand side of the rule, the state graphs that represent all effects of that action, thus modeling the outcome of its application. For instance, the rule corresponding to the action *aspirate lidocaine* of Table 2 can be seen in Fig. 6. Notice that all conditions listed for this action (conditions *a*, *b*, and *c* represented in Fig. 5(a)–(c), respectively) are present in the left-hand-side of the rule. Analogously, the right-hand-side of the rule in Fig. 6 presents the effect *d* (Fig. 5(d)) of that action.

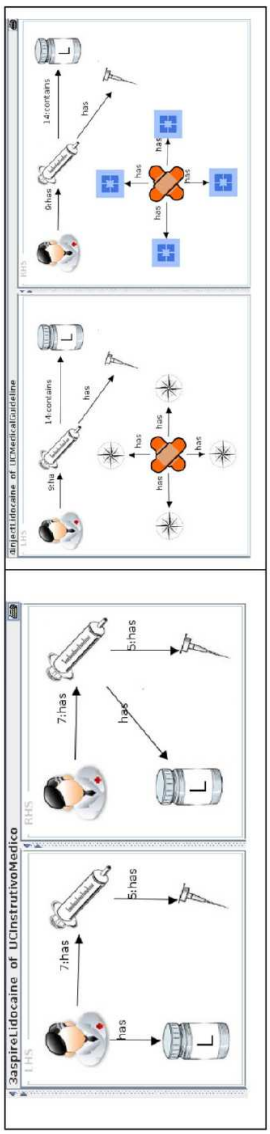
In some cases, the analyst can decide to group multiple steps of the Use Case in a single rule. This is the case, for example, of the iteration described in Steps 6–8 of Fig. 3. One possible way of modeling these actions is to have four rules, each one connecting *¼ of estimated volume of medication to* one different anesthetic button. Another possibility is to have a single rule representing Steps 6–8. This was the chosen option for this document. The analyst decided to focus only on the result of the complete medication infiltration, similarly to what is shown in Fig. 7(b).

Nonetheless, we recall that elements in the left side which do not appear in the right side are deleted by the rule application. In this particular case, the rule would not only have the effect of putting the lidocaine into the syringe, but also the collateral effects of deleting the MD, the needle and their relationships with the syringe. While in some cases the deletion is something to be desired, we would not expect, for example, that the MD disappears as an effect of aspiring the lidocaine into the needle. This is a typical modeling problem that may happen to less experienced analysts but that is easily detected during the analysis step.

Thus, the modeler can check, during this step, whether the elements deleted in a rule should in fact be deleted, in which case the rule remains as modeled. Otherwise, he/she adds these elements from the left side again in the right side, to ensure the desired semantics of the graph. Fig. 7(a) shows this kind of modification in the rule modeling the action *aspirate lidocaine*.

One important issue to be emphasized regarding the modeling is that the modeler is not always experienced enough or has enough knowledge to decide about what should or should not be deleted in a rule (when this is not explicitly mentioned in the UC). In this case, the modeler may leave the rule *as is* (assuming all deletions are correct) and any problems in this context will arise during the *conflict* or *dependency analyses*.

Step 6: Analysis: In this step, three automated verifications are



(a) aspiring 2% Lidocaine in the 5ml syringe **(b) injecting 2% Lidocaine in the infiltration points and forming the 4 anesthetic buttons**

Fig. 7. Rules representing two actions in the SOP for cutaneous leishmaniasis treatment.

performed over the generated GT model using AGG tool.[1] We present here examples of issues raised during these analyses and involving the actions presented in Table 2, as well as corresponding effects and solutions.

Conflict analysis: Fig. 6 shows a situation where an entity (the MD) is not preserved by a rule. The conflict analysis would show, in this case, a conflict between this rule with all other rules that have the MD existence as a condition (i.e., that require the MD entity in their left-hand side graph), such as the rule representing the *infiltrate lidocaine* shown in Fig. 7(b). The analysis would point out an unexpected conflict showing that the *infiltrate lidocaine* rule cannot be applied after the *aspirate lidocaine* rule (because one of its conditions does not hold), which clearly represents a mistake.

Conflicts must arise only when the Use Case has a decision point (an alternative or exceptional action) or the action must not be applied several times indefinitely. For example, the rule in Fig. 7(b) has an expected conflict with itself, because once the Lidocaine has been applied, the cardinal points of the injury turn into (or are replaced by) anesthetic buttons, thus changing the pattern in the left side in a way the rule cannot be applied anymore. This conflict means that "Lidocaine cannot be applied a second time", which is reasonable in the context of this Use Case.

Dependency analysis: In the example, a dependency between rules in Fig. 7 is expected, in the sense that the syringe must contain Lidocaine before this substance can be administered to the patient. Notice that the effect of the first rule (Fig. 7(a)) creates part of the conditions needed for the second one (Fig. 7(b)). If this kind of indication does not appear during the analysis, it means the script or the model did not enforce this pre-condition.

Rule sequence: In this analysis, a rule for each possible sequence of actions in the UC is automatically generated. Each of these sequences (rules) summarizes the conditions and effects of applying a certain sequence of actions of the UC. The left-hand side of a rule sequence shows all conditions that are not generated by any rule embedded in the sequence but that are required for the combined action to occur. Analogously, the right-hand side of the rule sequence shows the final state of the system after the combined action is executed. Thus, only instances of entities and relationships preserved (not deleted) or created by all embedded rules must appear in this final state of the rule sequence. For example, Fig. 8 shows a rule representing the application of the main path of the SOP in a single step. This rule represents the case where a single application of the medication leads to the lesion saturation.

This analysis is used to check whether the pre- and post-conditions of the UC as a whole are well defined. It also allows the identification of odd behaviors or inconsistencies that should not happen. For example, in the right side of Fig. 8 one can observe a single syringe connected to two needles and connected to two different medications. This means that, at the end of the medical procedure, the syringe is coupled to two needles at the same time and contains two different medications, which is not reasonable in the context of this Use Case. Notice that only one instance of the 25G × 0.7 mm needle is connected to the garbage whereas the second one and the insulin needle remain connected to the syringe. One can also observe that the ampoule is completely disconnected. Instead, it should be connected to the *garbage* entity (should be discarded during the procedure). This type of issue indicates ambiguity and/or omissions in the Use Case.

The complete list of possible Open Issues that can be identified by the verification methodology can be found at [10].

[1] AGG 2.0 (2011), http://tfs.cs.tu-berlin.de/agg.

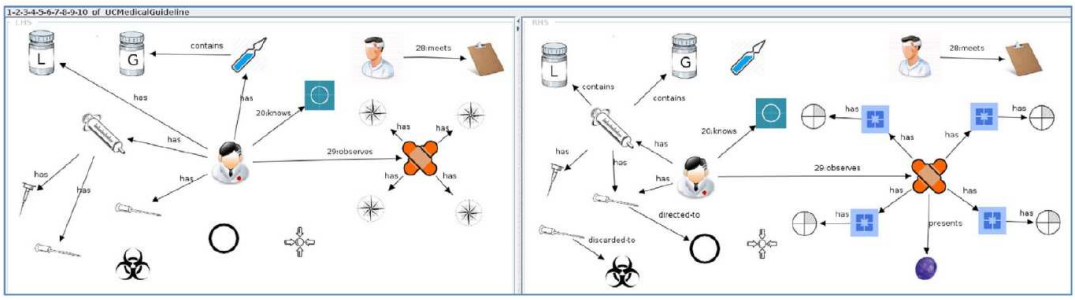


Fig. 8. Rule sequence representing the main flow of the SOP for cutaneous leishmaniasis treatment use case.

Table 3
Summary of Open Issues found during the verification process.

OI #	Open Issue	Time of detection	Action taken	Result
1	Use of synonyms (calculate/estimate)	Dependency analysis (first round)	Use a single word (estimate)	UC changed
2	Use of synonyms (medication/medicine/Glucantime)	Dependency analysis (first round)	Use a single word in all steps (Glucantime)	UC changed
3	Lack of explicit dependency between steps 3 and 4 (aspire and inject Lidocaine)	Dependency analysis (first round)	Rephrase step 4 to make dependency explicit	UC changed
4	Lack of explicit dependency between syringe and needle in steps 5 and 6	Dependency analysis (first round)	Rephrase step 5 to make dependency explicit	UC changed
5	Use of synonyms (needle/25G × 0.7 mm needle)	Dependency analysis (first round)	Use a single word in all cases (25G × 0.7 mm needle)	UC changed
6	One syringe is coupled to 2 needles	Rule sequence (first round)	Add pre-condition to the UC: required material	UC changed
7	Entity *needle* is connected to an entity *physician* instead of entity *syringe*	Rule sequence (first round)	Add pre-condition to the UC (required material) and change model	UC and model changed
8	Entity physician is connected to Glucantime ampoule	Rule sequence (first round)	Add pre-condition to the UC: required material	UC changed
9	Entity physician is connected to 2% lidocaine	Rule sequence (first round)	Add pre-condition to the UC: required material	UC changed
10	Glucantime ampoule remains active at the end of the procedure	Rule sequence (first round)	Add step to discard the Glucantime ampoule	UC changed
11	One syringe contains 2% lidocaine and Glucantime at the same time	Rule sequence (first round)	Solution of OI 6 solved this issue	UC changed
12	Physician observation results nothing	Rule sequence (first round)	Add post-conditions to the UC	UC changed
13	Ulcer state after procedure is undefined	Rule sequence (first round)	Add post-conditions to the UC	UC changed
14	there is a needle associated to the center of the ulcer	Rule sequence (first round)	Change model	Only model changed
15	Number of infiltration points is too restrictive	Author revision of the UC after first round	Rephrase corresponding steps	UC changed
16	Needle type is too restrictive in some steps of main scenario	Author revision of the UC after first round	Rephrase corresponding step	UC changed
17	Volume of Glucantime per anesthetic button is too restrictive	Author revision of the UC after first round	Rephrase corresponding steps	UC changed
18	extra volume of Glucantime is incorrect	Author revision of the UC after first round	Rephrase corresponding step	UC changed
19	Needle type in alternative scenario is too restrictive	Author revision of the UC after first round	Rephrase corresponding step	UC changed
20	Volume of 2% lidocaine not informed	Dependency analysis (second round)	Re-structure UC: add pre-conditions	UC changed
21	Alternative scenario is too generic	Rule sequence (second round)	Re-structure UC (division in more focused UCs)	UC changed
22	Volume of Glucantime is incorrect	Author revision after second round	Rephrase corresponding steps	UC changed
23	Sequence of instructions is inverted	Conflict analysis (third round)	Re-structure UC	UC changed

6. Results

6.1. Detected problems in the document

The UC generated by translating the original document presented 10 instructions (steps) in the main flow and 7 instructions to deal with alternative and exceptional flows, as shown in Fig. 3. Preparation steps were included as a set of pre-conditions. Although not present in the original SOP, a set of basic post-conditions was also included in the UC notation, as they would create notorious OIs. Fig. 4 shows the graph that mathematically models the SOP and results from the application of Steps 1–3 of the verification methodology. During the modeling

Name	Intralesional Infiltration Technique – **Part 1: Analysis of a single lesion**
Preconditions	- Patient meets treatment criteria - MD knows the maximum volume of Glucantime that can be administered to the patient per day
Postconditions	- Lesion is classified (*small* or *large)* - A number (*n*) of anesthetic buttons are defined and have been formed in the lesion (n = 1 for small lesions)
Primary Actor(s)	Physician (MD)

Step	Main Scenario Actions
1	MD evaluates the lesion and classifies it as *large*
2	MD defines the number (*n*) and location of the anesthetic buttons (points adjacent to the lesion from where Glucantime will be injected)
3	MD prepares the lesion for infiltration of Glucantime and creates the anesthetic buttons.
4	MD finishes analysis
5	Procedure continues in Part 2 – Infiltration
Step	**Alternative Actions**
1a1	MD evaluates the lesion and classifies it as *small*
1a2	MD prepares the lesion for infiltration of Glucantime and creates the single anesthetic button
1a3	Procedure continues on Step 4 of the Main Scenario

Fig. 9. Revised version of the SOP for cutaneous leishmaniasis treatment (in UC notation) after formal verification – part 1: analysis.

Name	Intralesional Infiltration Technique – **Part 2: Basic procedure: infiltration in small lesions**
Preconditions	- UC01 (Part 1 –Analysis of a single lesion) has been performed - MD knows the maximum volume of Glucantime that can be administered to the patient per day - Patient has not received a volume of Glucantime that exceeds the maximum recommended volume in a single day - Lesion has been classified as *small* - Lesion area has been prepared and a single anesthetic button has been formed in the lesion - Required material is available: (5-10ml) syringe with 25x0.7G needle, containing one ampoule (5mg) of Glucantime
Postconditions	- The lesion has a known status (*saturated* - presents edema - or *non-saturated*)
Primary Actor(s)	Physician (MD)

Step	Main Scenario Actions
1	MD inserts the 25x07G needle in the anesthetic button towards the center of the lesion and with the bevel facing up
2	MD retracts the 25x0.7G needle towards the border of the lesion and at the same time injects a minimal volume of Glucantime
3	MD observes that edema has formed in the whole lesion, including its center and borders (lesion is saturated).
4	MD discards all material and ends the procedure
Step	**Alternative Actions**
3a1	MD observes non-saturated regions in the lesion
3a2	Procedure continues on Part 4: Additional Infiltration

Fig. 10. Revised version of the SOP for CL treatment (in UC notation) after formal verification – part 2: basic Infiltration in small lesion.

process, the analysts tried to make as few assumptions as possible, aiming at creating a model as faithful as possible to the meaning

Name	Intralesional Infiltration Technique – **Part 3: Basic procedure: infiltration in large lesions**
Preconditions	- UC01 (Part 1 –Analysis of a single lesion) has been performed - MD knows the maximum volume of Glucantime that can be administered to the patient per day - Patient has not received a volume of Glucantime that exceeds the maximum recommended volume in a single day - Lesion has been classified as *large* - Lesion area has been prepared and a number *n* of anesthetic buttons have been formed in the lesion - Required material is available: (5-10ml) syringe with 25x0.7G needle, containing one ampoule (5mg) of Glucantime
Postconditions	- The lesion has a known status (*saturated* - presents edema - or *non-saturated*)
Primary Actor(s)	Physician (MD)

Step	Main Scenario Actions
1	MD estimates the volume of Glucantime to be injected from each anesthetic button (according to the area of the lesion reached by each one)
2	MD inserts the 25x07G needle in one anesthetic button towards the center of the lesion and with the bevel facing up
3	MD retracts the 25x0.7G needle towards the border of the lesion and at the same time injects the estimated volume of Glucantime for that anesthetic button.
4	MD repeats steps 3 and 4 for each remaining anesthetic button.
5	MD observes that edema has formed in the whole lesion, including its center and borders (lesion is saturated).
6	MD discards all material and ends the procedure
Step	**Alternative Actions**
5a1	MD observes non-saturated regions in the lesion
5a2	Procedure continues on Part 4: Additional Infiltration

Fig. 11. Revised version of SOP for CL treatment (in UC notation) after formal verification – part 3: basic Infiltration in large lesion.

implied by the text of the original document. Any assumption was registered as an OI to be confirmed with the authors of the SOP Table 3 summarizes all issues identified throughout the verification process of the SOP for cutaneous leishmaniasis treatment.

In the first round of analysis of the cutaneous leishmaniasis treatment model, a total of 14 OIs were raised and required modifications in the text and/or in the model. Some of these first issues were related to ambiguities present in the text of the original script that led to wrong assumptions. As an example, the word "medication" was used to refer to both, 2% Lidocaine and Glucantime® (OI #2 in Table 3). Although a specialist can infer which exact medication was meant in each statement of the document, the word did cause misunderstandings for the analysts, and the same mistake could happen with less attentive or less experienced physicians. Another issue worth mentioning is related to the material used in the procedure. In one step, it is not clear whether the same syringe or a new one is used (OI #6 in Table 3). This problem appeared in the formal model as the lack of dependency between a rule that discards the material used and the one the uses the same material, which precluded the generation of the Rule sequence corresponding to the Main Scenario of the UC. Such ambiguities were removed from the SOP to avoid any possible misunderstanding of the treatment instructions. A third problem that arose during this first analysis is related to the preparation steps and required material for the treatment, which were not listed in the original script but must be included as pre-conditions for the modeled medical procedure.

Based on the Open Issues raised in the first verification round, a second (documented) version of the UC was generated and sent to the authors for their perusal and confirmation. This manual revision raised 5 new issues detected by the authors of the SOP (OIs #15 to #19 in Table 3). Some issues identified at this point originated from the

Name	Intralesional Infiltration Technique – **Part 4: Additional Infiltration**
Preconditions	- UC02 or UC03 (Basic Infiltration) has been performed - Lesion´s state is *non-saturated* - Volume of Glucantime already injected in the patient in this intervention is known and does not exceed the maximum recommended volume - Required material is available: (5-10ml) syringe with 25x0.7G needle containing Glucantime
Postconditions	- Non-saturated regions of the lesion received additional volume of medication required to achieve saturation - Patient received the volume of medication required to saturate the lesion or the maximum volume of Glucantime per day has been achieved - Total volume of injected Glucantime for this lesion is known - Final state of the lesion is known (*saturated* or *non-saturated*)
Primary Actor(s)	Physician (MD)

Step	Main Scenario Actions
1	MD identifies the anesthetic buttons from which additional Glucantime will be injected
2	MD inserts the 25x07G needle of the syringe with Glucantime in one of the identified anesthetic buttons towards the center of the lesion and with the bevel facing up
3	MD retracts the 25x0.7G needle towards the border of the lesion and at the same time injects a minimal volume of Glucantime (volume is defined according to the area covered by this anesthetic button)
4	MD register the volume of Glucantime injected in Step 3.
5	MD evaluates that the total volume of Glucantime already injected in this patient during this intervention is below the maximum recommended volume.
6	MD repeats steps 2 to 5 for each remaining anesthetic button identified in Step 1.
7	MD observes saturation (edema has formed) in the whole lesion, including its center and borders.
8	MD registers the total volume of Glucantime injected in this lesion
9	MD discards all material and ends the procedure
Step	**Alternative Actions**
7a1	MD observes non-saturated regions in the lesion
7a2	MD evaluates that the total volume of Glucantime already injected in this patient during this intervention is below the maximum recommended volume
7a3	Procedure continues on Step 1 of the Main Scenario
Step	**Exception Actions**
5a1	The maximum recommended volume of Glucantime per day has been achieved
5a2	Procedure continues on Step 8 of the Main Scenario

Fig. 12. Revised version of the SOP for CL treatment (in UC notation) after formal verification – part 4: Additional infiltration.

attempt to remove ambiguities during the modeling step (a few sentences of the UC were modified to better reflect the defined model). For instance, the original SOP assumes a typical cutaneous leishmaniasis ulcer which has an oval shape. As a result of the first analysis, some sentences stressed this ulcer format thus calling the author's attention to possible different scenarios such as different ulcer sizes and shapes (OI #15). Even though a physician is supposed to identify and adjust the procedure accordingly, leaving these scenarios out of the scope of the SOP may result in non-determinism in the application of the procedure, which goes against the proposed standardization. In another example, the distribution of Glucantime among anesthetic buttons was ill-defined (OI #17). By reviewing structured sentences, the authors became aware of such omissions or ambiguous instructions of the original script. The revised version of the UC was then re-modeled and submitted to a second round of analyses.

During the second verification round, 2 new issues were raised and

Name	Intralesional Infiltration Technique – **Part 1: First Infiltration**
Preconditions	- MD knows the maximum volume of Glucantime that can be administered to the patient per day - Patient has not received a volume of Glucantime that exceeds the maximum recommended volume in a single day - Lesion area has been cleaned - Required material is available: (5-10ml) syringe with 25x0.7G needle, containing one ampoule (5mg) of Glucantime
Postconditions	- The lesion has a known status (*saturated* - presents edema - or *non-saturated*)
Primary Actor(s)	Physician (MD)

Step	Main Scenario Actions
1	MD defines the number (*n*) and location of the anesthetic buttons (points adjacent to the lesion from where Glucantime will be injected)
2	MD prepares the lesion for infiltration of Glucantime and creates the anesthetic buttons.
3	MD inserts the 25x07G needle in one anesthetic button towards the center of the lesion and with the bevel facing upwards
4	MD retracts the 25x0.7G needle towards the border of the lesion and at the same time injects the Glucantime ((injected volume is proportional to the area covered by this anesthetic button)
5	MD repeats steps 1 and 2 for each remaining anesthetic button.
6	MD observes that edema has formed in the whole lesion, including its center and borders (lesion is saturated).
7	MD discards all material and ends the procedure
Step	**Alternative Actions**
6a1	MD observes non-saturated regions in the lesion
6a2	Procedure continues on Part 2: Additional Infiltration

Fig. 13. Revised SOP for cutaneous leishmaniasis treatment (in UC notation) after experts validation phase – part 1.

the script was modified accordingly once again. Issues raised in this round were related to omission of information: the volume of 2% Lidocaine to be injected in the lesion is not defined (OI #20) and the alternative scenario was too generic (the corresponding "rule sequence" could not be defined–OI #21). In most cases, errors of omission occur because a certain tacit or technical knowledge is assumed in the document. Such omissions can lead to problems when this assumption is frustrated, which can happen with less experienced physicians or health agents working under any kind of pressure. Those issues were resolved by the authors of the SOP, since they are related to technical knowledge. In the case of the 2% Lidocaine issue, for instance, the authors judged that this is indeed common knowledge and its inclusion in the SOP would not be beneficial. However, for the alternative scenario, they opted for the revision of the text. Furthermore, the revised script generated after the second round contained a possibly over-specified instruction that was detected and corrected by the authors (OI #22).

After the second round of analysis, the text of the SOP became clearer and the next verification round raised a single issue related to the structure of the text and the procedure itself. The original text (Fig. 1) is an unstructured document and some instructions are described after an action that in fact depends on that instruction. For example, Step 7 in Fig. 1 instructs the physician to divide the volume of medication among all infiltration points. However, up to this point, there is no instruction indicating how to calculate the volume of medication. Furthermore, constraints about the maximum volume of medication that can be administered to a patient appear as a comment (Observation 2) in Fig. 1, although it may affect the normal execution flow of the procedure. By analyzing the dependency among rules in the formal model, those issues were raised and brought to the attention of the SOP's authors. Indeed, the structure of the original document requires that the physician reads and memorizes the whole procedure before starting the intervention. This modus operandi might reduce the adherence to the SOP as usual distractions during the intervention can easily lead to mistakes in terms of volume of medication, injection procedure, etc. Hence, based on those issues, we suggested a structural

Name	Intralesional Infiltration Technique – **Part 2: Additional Infiltration**
Preconditions	- UC01 (Part 1 – First Infiltration) has been performed - Lesion´s state is *non-saturated* - Volume of Glucantime already injected in the patient in this intervention is known and does not exceed the maximum recommended volume - Required material is available: (5-10ml) syringe with 25x0.7G needle containing Glucantime, extra ampoules of Glucantime
Postconditions	- Non-saturated regions of the lesion received the minimum additional volume of medication required to achieve saturation - Patient received the minimum volume of medication required to saturate the lesion or the maximum volume of Glucantime per day has been achieved - Total volume of injected Glucantime for this lesion is known - Final state of the lesion is known (*saturated* or *non-saturated*)
Primary Actor(s)	Physician (MD)

Step	Main Scenario Actions
1	MD identifies the anesthetic buttons from which additional Glucantime will be injected
2	MD inserts the 25x07G needle of the syringe with Glucantime in one of the identified anesthetic buttons towards the center of the lesion and with the bevel facing upwards
3	MD retracts the 25x0.7G needle towards the border of the lesion and at the same time injects a minimal volume of Glucantime (injected volume is defined according to the area covered by this anesthetic button)
4	MD register the additional volume of Glucantime injected from this anesthetic button
5	MD evaluates that the total volume of Glucantime already injected in this patient during this intervention is below the maximum recommended volume.
6	MD repeats steps 2 to 5 for each remaining anesthetic button identified in Step 1.
7	MD observes saturation (edema has formed) in the whole lesion, including its center and borders.
8	MD registers the total volume of Glucantime injected in this lesion
9	MD discards all material and ends the procedure
Step	**Alternative Actions**
7a1	MD observes non-saturated regions in the lesion
7a2	MD evaluates that the total volume of Glucantime already injected in this patient during this intervention is below the maximum recommended volume
7a3	Procedure continues on Step 1 of the Main Scenario
Step	**Exception Actions**
5a1	The maximum recommended volume of Glucantime per day has been achieved
5a2	Procedure continues on Step 8 of the Main Scenario

Fig. 14. Revised SOP for cutaneous leishmaniasis treatment (in UC notation) after experts validation phase – part 2.

modification of the SOP text.

The original 1-page SOP was transformed into a more detailed script composed of four parts: (1) Initial procedure: lesion analysis; (2) Basic procedure: infiltration in small lesions (≤ 1 cm); (3) Basic procedure: infiltration in large lesions (> 1 cm); and (4) Additional procedure: additional infiltration in case of non-saturated lesions. This modified document is shown in UC notation in Figs. 7–10 respectively.

Each UC from Figs. 9–12 was re-modeled and re-verified, and no major OIs were raised. Thus, after four verification rounds, we achieved a more precise SOP that covers many possible scenarios that can be faced by the physician during the intervention. The scripts created from each UC presented the instructions in such a way that it is easier to the physician to adhere to the standard and collect meaningful data for the further validation of the proposed treatment.

6.2. Evaluation and scope of the formal verification

In order to assess the reliability of the procedure guide after its formal verification and improvements we performed a pre-clinical validation study. In this pilot project, ten intralesional infiltration procedures following the revised instrument were performed and analyzed. One investigator and one trained nurse observed the interventions in order to identify: actions performed during the procedure that are not described in the instrument; actions described and not performed or performed differently. The results were discussed with three other medical professionals involved in regular execution of the procedure. We observed that although unambiguous and clear, the revised document had too much detail and redundant information in each instruction. Indeed, tacit knowledge was made explicit in the document during the verification procedure. The authors of the intervention can, however, decide whether this information can be omitted, considering the expected profile of the users of the document. If the authors opt for the omission of some information, they are prioritizing the readability of the document over its completeness. This should be a conscious, informed decision, based on the evaluation the risks involved in leaving some information out. The formal verification process helps the authors to make such an evaluation: it forces the inclusion of all information required to ensure the correctness of the guide. Then, the authors can carefully and consciously remove the redundant ones.

Another issue raised during this informal inspection done by experts is related to the scope of the proposed standardization instructions. The original SOP (and the generated model) had included instructions for the preparation of the patient and of the lesion area. Those instructions were detailed after the verification procedure. Then, during the validation procedure, physicians were able to pinpoint the exact instructions that were redundant (such as the ones about anesthesia) and the ones that were really about the new standard.

A third issue raised during the validation in the field is related to the medical procedure itself. The original division between small and large lesions (explicated in Figs. 10 and 11 respectively) has shown to be invalid and was removed from the document.

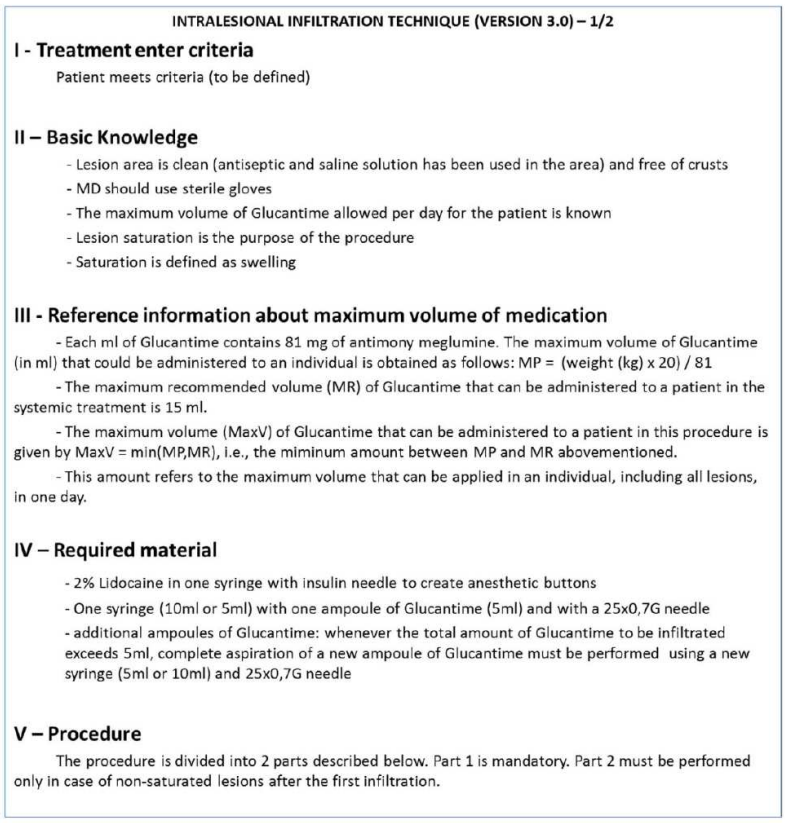
After the applicability analysis carried out by the health professional team, the SOP was revised once again and simplified, generating a document divided in only two parts: (1) First infiltration; and (2) Additional infiltration, as shown, respectively, in Figs. 13 and 14 (UC notation). Fig. 15 depicts de final script in textual format.

In summary, the comparison between the formal and informal methods, applied to the quality inspection of the SOP for cutaneous leishmaniasis treatment, revealed that the two processes are complementary, identifying different types of faults. The formal verification recognizes more efficiently problems of ambiguity, inconsistency and omissions, offering agility and systematization to the content validation process. On the other hand, the analysis carried out informally by experts is able to ensure the comprehensiveness and technical accuracy of the document while taking into account the human aspects that impact, for instance, adherence to the proposed guide. In addition, there will always be ethical and technical decisions that can only be evaluated and defined by experts on the subject taking into account the latest knowledge (Fig. 16).

7. Final remarks

We have proposed the use of a formal verification methodology to improve the content validation process of a medical SOP document.

The proposed verification strategy aims at detecting faults that are typical to artefacts written in natural language, such as omission and ambiguity. The methodology consists in modeling the medical document using graph transformation formalism and performing semi-automatic analyses over the generated model. Such analyses raise possible issues in the document that may affect its correctness and completeness, thus providing valuable information to the SOP's authors. The main advantage of the proposed method is the systematization of a process in order to ensure that all aspects required in the verification



INTRALESIONAL INFILTRATION TECHNIQUE (VERSION 3.0) – 1/2

I - Treatment enter criteria

Patient meets criteria (to be defined)

II – Basic Knowledge

- Lesion area is clean (antiseptic and saline solution has been used in the area) and free of crusts
- MD should use sterile gloves
- The maximum volume of Glucantime allowed per day for the patient is known
- Lesion saturation is the purpose of the procedure
- Saturation is defined as swelling

III - Reference information about maximum volume of medication

- Each ml of Glucantime contains 81 mg of antimony meglumine. The maximum volume of Glucantime (in ml) that could be administered to an individual is obtained as follows: MP = (weight (kg) x 20) / 81
- The maximum recommended volume (MR) of Glucantime that can be administered to a patient in the systemic treatment is 15 ml.
- The maximum volume (MaxV) of Glucantime that can be administered to a patient in this procedure is given by MaxV = min(MP,MR), i.e., the miminum amount between MP and MR abovementioned.
- This amount refers to the maximum volume that can be applied in an individual, including all lesions, in one day.

IV – Required material

- 2% Lidocaine in one syringe with insulin needle to create anesthetic buttons
- One syringe (10ml or 5ml) with one ampoule of Glucantime (5ml) and with a 25x0,7G needle
- additional ampoules of Glucantime: whenever the total amount of Glucantime to be infiltrated exceeds 5ml, complete aspiration of a new ampoule of Glucantime must be performed using a new syringe (5ml or 10ml) and 25x0,7G needle

V – Procedure

The procedure is divided into 2 parts described below. Part 1 is mandatory. Part 2 must be performed only in case of non-saturated lesions after the first infiltration.

Fig. 15. Final SOP for cutaneous leishmaniasis treatment – part 1: basic knowledge.

were observed and corrected, independently of previous knowledge and subjective interpretations. Furthermore, in the context of computerized guidelines, the verified Use Case generated by our strategy can serve as a high-quality specification artefact for future automation of a medical standard. The following advantages of the proposed verification methodology are also worth mentioning: it uses free computer software; it requires only basic knowledge about the used formalism; it does not require synchronous revision meetings during the verification process since the authors of the document are consulted about very specific points; medical experts receive a more mature and reliable document to evaluate and can focus on the technical aspects of the SOP. For those reasons, we believe this can be a cost-effective solution for content validation.

To complete the content validation of the health instrument, the formal verification is followed by a traditional informal validation procedure, where medical experts evaluate the technical aspects of that instrument. Moreover, the experts were able to focus their analysis in the technical aspects of the document without compromising its clarity.

The proposed approach was applied to a SOP for intralesional cutaneous leishmaniasis treatment that is currently under development. It was possible to identify a considerable number of problems that could otherwise remain unknown and might compromise the applicability of that script. The formal verification led to an updated SOP that is less ambiguous than the original one and considers several possible treatment scenarios, increasing its applicability and reliability.

Possible future developments for this work include a comparative analysis of overall costs of validation processes (formal and informal ones) as well as a qualitative evaluation of the final document in comparison to its first draft.

We presented an example of validation of a new therapeutic approach for cutaneous leishmaniasis but this tool can be adapted and used for the validation of other types of documents and processes, such as diagnostic procedures and other routines and treatments in health care settings.

Despite our promising results, the proposed approach has a few limitations: the generation of the formal model is still a manual task, although a systematic one. One possible solution to this problem is the use of UMLS or other standard naming databases to automate the first step of the methodology (identification of entities). In another direction, in environments supported by electronic health systems, one can evaluate the use of domain-specific languages for the description of the SOP instructions as to allow the automatic translation from the document to a formal model, as proposed in [24,25]. A second limitation is related to the type of problems that can be detected in the document, which is related to the type of analysis currently performed in the verification methodology. Our current work is addressing this problem by implementing additional analysis in the verification tool.

Contributors

Dr. Érika Cota proposed the use of the formal verification strategy to the health instrument and served as bridge between the computer science and medical teams. She participated in the formal verification

INTRALESIONAL INFILTRATION TECHNIQUE (VERSION 3.0) – 2/2

V – Procedure

Part 1) First infiltration

1) Analyze the lesion and define the number and position of the required anesthetic buttons. Use as many anesthetic buttons as deemed necessary according to the shape of the lesion. For a typical oval lesion, it is suggested that anesthetic buttons be located at the four cardinal points of the lesion (see figure below).

2) Perform the injection of 2% Lidocaine to form all anesthetic buttons defined in Step 1. The puncture occurs in the healthy skin adjacent to the lesion, with 30° tilt.
3) Infiltrate Glucantime using the following technique: insert the 25x07G needle from one anesthetic button towards the center of the lesion and with the bevel facing up
4) Retract the 25x0.7G needle towards the border of the lesion while gently injecting the Glucantime (injected volume is proportional to the area covered by this anesthetic button)
5) Repeat steps 3 and 4 for each remaining anesthetic button
6) Observe the lesion and check whether there is saturation of the entire lesion, including base/bottom and edges
7) If the entire lesion is saturated, end the procedure and apply a dressing.
8) If the lesion presents non-saturated regions, proceed with Part 2 – Additional Infiltration

Part 2) Additional Infiltration (non-saturated lesions)

9) Identify the anesthetic buttons from which additional Glucantime will be injected, i.e., the ones closest to non-saturated regions of the lesion
10) Insert the 25x07G needle in one of the identified anesthetic button towards the center of the lesion and with the bevel facing upwards
11) Retracts the 25x0.7G needle towards the border of the lesion while gently injecting *a minimal* volume of Glucantime (injected volume is proportional to the area covered by this anesthetic button)
12) Register the additional volume of Glucantime injected from this anesthetic button
13) If the total volume of Glucantime already injected in this patient during this intervention is below the maximum recommended volume (MaxV), perform steps 10 to 12 for each remaining anesthetic button identified in Step 9. Otherwise, register the total volume of Glucantime injected in this lesion and proceed to Step 14.
14) Observe the lesion and check whether there is saturation of the entire lesion, including base/bottom and edges
15) If lesion is saturated, register the total volume of Glucantime injected in this lesion and end the procedure.
16) If there are non-saturated regions in the lesion and the total volume of Glucantime already injected in this patient during this intervention is below the maximum recommended volume (MaxV), proceed from Step 9 until lesion is saturated or maximum recommended volume of Glucantime has been administered, whichever happens first.

Fig. 16. Final SOP for cutaneous leishmaniasis treatment – part 2: proposed procedure.

process and also led the production of this article. Dr. Leila Ribeiro led the verification process itself, with her expertise in the Graph Transformation formalism. Jonas Bezerra and Andrei Costa carried out the verification process of the CL guideline, generating the models and conducting all the analyses. Rosiana da Silva is a co-author of the CL treatment guideline and participated in the informal validation process. Dr. Gláucia Cota leads the medical team responsible by the medical guideline and helped in the verification process by providing feedback about the raised issues as well as changing the guideline document. She also made significant contributions to the conceptualization of the article and review and synthesis of the literature. All authors contributed with content, critical review, and revision of the manuscript.

Competing interests

The authors have no competing interests to declare.

Summary points

What was already known on the topic?

- Content validation of treatment standardization procedures results from the perusal of different expert examiners. It is an informal process that focuses on the technical aspects of the proposed treatment. Revisions are based on aspects intuitively identified by observers, based on their previous knowledge and individual experience with the subject in question.
- A medical standard procedure written in natural language is prone to non-technical problems such as omissions, ambiguities, and wrong information, among others, that may compromise its understanding and adherence. Many of those problems may be overlooked during the content validation phase.
- Software specification artefacts written in natural language are also prone to omissions, ambiguities, etc. and many formal and informal verification strategies have been proposed to tackle those errors.

What does this study add to our knowledge

- We propose to divide the content validation phase of a standard medical operation procedure in two parts: (i) the verification

of the document using a formal method, and (ii) the manual review by experts.

- We show that the formal verification of the document identified a number of issues that could compromise adherence to a treatment standardization procedure but were not detected by the traditional content validation strategy.
- The proposed semi-automatic verification approach guides the revision of the document by exposing several potential problems and leading the authors of the document to take informed decisions about the content and structure of the document.
- We show that the two validation processes (formal and informal) are complementary, identifying different types of faults. The formal verification recognizes more efficiently problems of ambiguity, inconsistency and omissions, offering agility and systematization to the content validation process. On the other hand, the analysis by experts is able to ensure the comprehensiveness and technical accuracy of the document, as well as the human aspects that also impact adherence to the proposed guide.

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Towards a standard protocol for antimony intralesional infiltration technique for cutaneous leishmaniasis treatment

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Towards a standard protocol for antimony intralesional infiltration technique for cutaneous leishmaniasis treatment

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BACKGROUND Despite its recognised toxicity, antimonial therapy continues to be the first-line drug for cutaneous leishmaniasis (CL) treatment. Intralesional administration of meglumine antimoniate (MA) represents an alternative that could reduce the systemic absorption of the drug and its side effects.

OBJECTIVES This study aims to validate the standard operational procedure (SOP) for the intralesional infiltration of MA for CL therapy as the first step before the assessment of efficacy and safety related to the procedure.

METHODS The SOP was created based on 21 trials retrieved from the literature, direct monitoring of the procedure and consultation with experts. This script was submitted to a formal computer-aided inspection to identify readability, clarity, omission, redundancy and unnecessary information (content validation). For criterion and construct validations, the influence of critical condition changes (compliance with the instructions and professional experience) on outcome conformity (saturation status achievement), tolerability (pain referred) and safety (bleeding) were assessed.

FINDINGS The median procedure length was 12 minutes and in 72% of them, patients classified the pain as mild. The bleeding was also classified as mild in 96.6% of the procedures. Full compliance with the SOP was observed in 66% of infiltrations. Despite this, in 100% of the inspected procedures, lesion saturation was observed at the end of infiltration, which means that it tolerates some degree of modification in its execution (robustness) without prejudice to the result.

CONCLUSIONS The procedure is reproducible and can be used by professionals without previous training with high success and safety rates.

Key words: cutaneous leishmaniasis - therapy - meglumine antimoniate - intralesional infiltration - validation

Cutaneous leishmaniasis (CL) is an endemic zoonosis transmitted by the bite of infected sandflies that causes lesions on exposed parts of the body and that has the potential to leave scars for life. Approximately two-thirds of all cases are concentrated in six countries: Afghanistan, Algeria, Brazil, Colombia, the Islamic Republic of Iran and the Arab Republic of Syria and, according to World Health Organization records, the number of CL cases tripled in high-burden countries from 1998 to 2014 (from > 50,000 in 1998 to approximately 150,000 in 2014) (WHO 2016). In total, cutaneous and visceral leishmaniasis are responsible for more than 3,300,000 days lost or days where some disability was experienced disability - adjusted life years (DALY) (Murray et al. 2012).

Despite its recognised toxicity, antimonial therapy has been employed for several decades and continues to be the first-line drug for CL treatment in many countries (WHO 2010). Intralesional administration of meglumine antimoniate (MA) represents an alternative that could reduce the systemic absorption of the drug and its side effects. Although widely used in the Old World, in the Americas, the experience with this therapeutic modality is still limited (Oliveira-Neto et al. 1997, Soto et al. 2013). The accumulated experience with the intralesional approach in Brazil suggests the efficacy and safety of the procedure. However, there are few detailed descriptions available for the intralesional technique, and there are several procedure variations, which makes it difficult to compare results, and thus, the implementation of this technique on a large scale is limited. In the past decade, the evidence basis for how processes of care affect outcomes have solidified, evolving in parallel with the concept of evidence-based medicine. In this context, the incorporation of this new therapeutic approach first requires its validation as a standardised process. The present study aims to develop and validate a tool to guide the MA intralesional infiltration procedure for CL treatment, a standard operational procedure (SOP). The process of developing and validating a set of instructions that guides the execution of the infiltration procedure will be the focus of this paper, which will not present data on the efficacy of the treatment itself, since it would require the analysis of other clinical parameters that are beyond the scope of this study.

SUBJECTS AND METHODS

The intralesional infiltration SOP was developed following a comprehensive and progressive process, and

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the ordered pool of instructions (script) built to guide the procedure was submitted to a series of rigorous tests of reliability based on the analyses of content, criterion and construct. Considering the intralesional infiltration a medical procedure and, as such, an action encompassing both understanding and knowledge, to validate the SOP, we chose to apply the psychometric principles (Beard et al. 2011) associated with automated methods of software inspection (Ribeiro et al. 2014).

Study phase I: the development of the SOP - As the first step, a systematic search of all descriptions of the procedure available in the MEDLINE and LILACS databases was performed in July 2015 using a sensitive strategy combined by Boolean operators. There was no language restriction, but the research was limited to the last 10 years, and the filter "clinical trial" was used. Additional studies were located by a manual search using references from retrieved papers, and trial register databases were also consulted. All identified studies were read in full focusing on the description of the intralesional procedure, specifically: anesthesia use; needle gauge specification, tilt, direction and depth during the infiltration; drug volume infiltrated or any criteria used for stopping the infiltration.

In addition, to identify all the stages comprising the intralesional infiltration process, an observation of the procedure being performed by an experienced professional in a specialised CL centre was also performed. However, even with these attempts (theoretical and practice) of gathering and sorting all actions necessary to carry out the infiltration, it was observed that there were still many conflicting or unresolved questions in the set of instructions. So, a panel of expert investigators with wide experience in the infiltration technique was consulted on the unsolved issues. All principal investigators in those published studies were identified and were contacted electronically and invited to answer a multiple-choice questionnaire. The investigators could also make any comment that they judged necessary. In the case of more than one publication from the same group, contact was made with the group coordinator, often identified as the last author on the manuscripts. Consultation with experts ended the first phase of this work, which resulted in the development of the first intralesional infiltration SOP version (script). An overview of the development and validation process is shown in a flowchart in Fig. 1.

Study phase II: validation of the first SOP version (script) - The reliability of the intralesional infiltration SOP was measured using the generalisability psychometric theory in a second study phase, where the content, criterion and construct aspects were validated (Beard et al. 2011, Raza et al. 2015). In other words, the assessment of reliability included the following aspects: (i) the internal consistency of the script (content validation); (ii) its stability to changes in critical conditions (criterion validation); (iii) the measurement of the extent to which the SOP leads to the intended result (construct validation).

The content validation of the intralesional infiltration script was performed systematically by a specific software product and is detailed in the Content Validation section. This computer-aided process identified several issues in the set of instructions, which were translated into queries by computer scientists and answered by the medical team. This interactive process generated after several rounds a reviewed and improved version of the script, now renamed SOP, which was implemented as the operational procedure to be followed during an ongoing clinical study addressing the efficacy and safety of AM intralesional therapy. The clinical study was submitted and approved by the Ethical Review Board of Centro de Pesquisas René Rachou (CPqRR), FIOCRUZ (approval

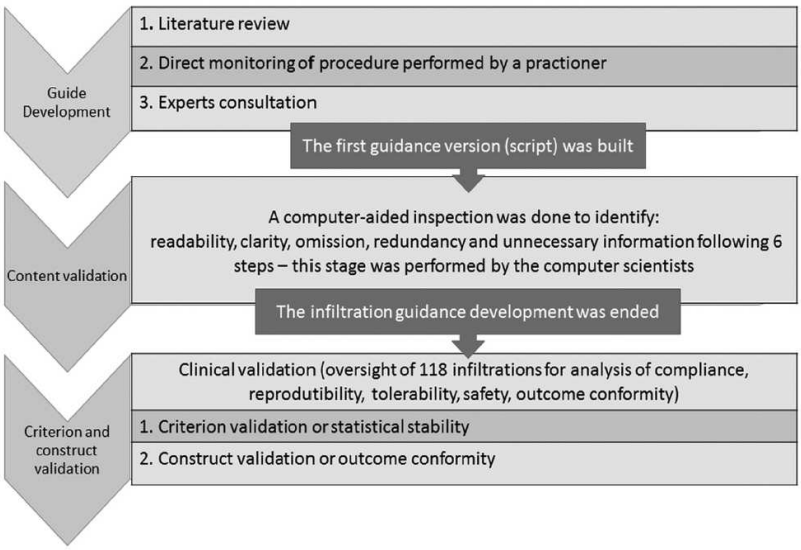

Fig. 1: flowchart of standard operational procedure development process.

number 1.136.132). In addition, the study protocol was registered on the Brazilian Clinical Studies Registry Database (REBEC) under number RBR-44KG5X.

A total of 17 medical doctors participated in the study. Initially, only three professionals with previous experience in intralesional infiltration (medical doctor seniors - permanent members of the clinic staff) performed the procedure. After six months, 14 training doctors (temporary staff: one month infectious diseases training residents) could also run the infiltration after reading the SOP. For criterion and construct validation, all the intralesional infiltration procedures were inspected by a single observer who filled out a checklist containing questions about the professional's adherence to the SOP and other features of the procedure, including a numeric visual scale of pain suffered by the patient.

Content validation - Content validation refers to the judgment of the quality of the description of the tool (script) or, in other words, if it covers all the actions included in the proposed procedure (intralesional infiltration) and does not contain elements (or actions) related to other procedures. A formal content evaluation method (Ribeiro et al. 2014) - a previously validated tool for verification of software specification documents - was applied (Cota et al. 2017). This method was developed by computer scientists from Federal University of Rio Grande do Sul, Brazil, and it is based on six steps:

Step 1: Pre-processing of the original script - This step consists of translating the first SOP version (script) to a computer notation where each action corresponds to one instruction in the procedure.

Step 2: Identification of entities - Consists of identifying the entities that appear in the script. Usually, the entities in a document are represented by nouns or noun phrases, such as "*medical doctor*", "*2% lidocaine*", "*syringe*".

Step 3: Identification of actions - The next step is to identify the essential actions to be performed separately. Actions are usually represented by verbs and verb phrases and correspond to operations involving the entities. The first step of the methodology makes this step simpler as one can extract one action for each translated instruction.

Step 4: Characterisation of conditions and effects as states - This is the modeling step, where the script written in natural language (medical terms) is described using mathematical notation. After extracting the entities and actions presented in the script, graphical representations for each one of them were defined to facilitate the visualisation of the mathematical model. Each part of the graphic is an element of a graph transformation (GT) model, i.e., a mathematical structure composed of nodes and arcs with an associated semantic that will be the target of further analysis steps.

Step 5: Construction of rules - This step consists of creating transition rules for each action listed in Step 3. A rule for an action is modeled as a transition between two states modeled in Step 4.

Step 6: Analysis - With all those artifacts built in the previous steps, several automatic analyses are performed to detect problems with the script. The "conflict analysis", "dependency analysis" and "rule sequence analysis" can raise open issues (OIs) regarding either some aspect of the instructions or the modeling.

Criterion validation - Criterion validation indicates the degree to which changes in process/performer influence the outcome; in this case, the outcomes were saturation status achievement and tolerability (scale of pain referred and bleeding score) and the critical conditions are the lack of adherence to the instructions provided in the SOP and professional experience. The statistical stability (robustness) of the tool was established by determining the inter-rater (comparison between the professionals) and test-retest (consistency of scoring over time) reliabilities. A structured questionnaire (checklist) with ten questions covering the essential actions and concepts (domains) considered essential to the achievement of the planned outcome (Supplementary data, Figure) was developed. The checklist was filled in by only one observer (study investigator) to identify whether a planned action was executed, if it was executed correctly, incorrectly or semi-correctly and if it was carried out in the sequence described. During the inspection of infiltrations, the study investigator asked the executor of the procedure (medical doctor) to inform which criterion he/she used to suspend the infiltration. When the executor finished the procedure, the study investigator evaluated whether the saturation state had been reached according to the previously adopted criterion: volume increase of the entire lesion, with or without pallor. Thus, with the checklist, a score from 0 to 10 indicating the degree of adherence to the instructions provided in the SOP was obtained. For assessment of the pain referred by the patient during the procedure, the visual analogue scale (VAS) (Gift 1989), an illustrated and continuum scale comprised of a horizontal line ranging from none to an extreme amount of pain defined as 10, was applied. For the bleeding assessment, the Fromme-Boezaart modified scale (Boezaart et al. 1995), a surgical field bleeding scale from 0 to 5 that is in accordance with blood cleaning requirements, was used. This scale was proposed for evaluation of surgical sites using the suctioning requirement as the bleeding intensity measurement. Suctioning is a kind of procedure not performed in outpatient setting, scenario of the intralesional infiltration. Even so, the score is easy to be applied and has been modified, being "suctioning" replaced by "bleeding removed by gauze".

Construct validation - The aim is to demonstrate that the process produces the planned result, namely, that the result obtained conforms to predetermined "target". The variables chosen for construct validation included the saturation status achievement at the end of infiltration, following the definition established by the consultation of experts; the tolerability of the procedure, as evaluated by the visual analogue scale of pain; and safety, as evaluated by the bleeding score.

Statistical analysis - The sample (number of infiltrations to be observed in reliability assessment) was determined considering a confidence level of 95% ($Z = 1.96$) and a maximum error margin of 20% for all domains

of interest (dichotomous data). Based on that, a sample of 24 procedures was estimated for each group for all comparisons necessary for the evaluation of statistical stability (experienced versus not experienced professionals, same professional's group over time), and the minimum number of intralesional infiltrations requested for the procedure validation was calculated as 72. Descriptive statistics were calculated for different groups in each domain. Statistical analysis was conducted using the Student's *t*-test, analysis of variance, the Wilcoxon signed-rank test (for nonparametric variables), chi-square, McNemar test (two related dichotomous variables) and One-Way ANOVA, whenever appropriate. The Spearman correlation coefficient and the 95% confidence interval (95% CI) for the correlation coefficient was used to compare the professional's adherence to the SOP according to their experience status. A logistic regression analysis model (using backward stepwise) for bleeding intensity was built adjusting covariates identified by univariate analyses with a $p < 0.2$. Statistical significance was set at the 0.05 level. All analyses were performed using Statistical Product and Service Solutions, IBM - SPSS® (version 23, California, USA).

RESULTS

Through literature review, 19 (Firooz et al. 2005, Shazad et al. 2005, Negi et al. 2007, Munir et al. 2008, Layegh et al. 2009, El-Sayed & Anwar 2010, Kashani et al. 2010, Van Thiel et al. 2010, Meymandi et al. 2011, Safi et al. 2012, Bumb et al. 2013, Khatami et al. 2013, Mohammedzadh et al. 2013, Soto et al. 2013, Dieterle & Pillekamp 2014, Stahl et al. 2014, Banihashemi et al 2015, Parizi et al. 2015, Ranawaka et al. 2015) clinical trials addressing intralesional therapy over the last 10 years were identified. Two additional studies, references from primary articles, were also included in the analysis (Oliveira-Neto et al. 1997, Zeglin 2009), totalising 21 studies reviewed.

The studies were performed between 2005-2015, mostly in the Old World, namely, in Iran (9), Afghanistan (5) India, (2) Sir Lanka (1), Pakistan (1), Egypt (1), Bolivia (1), and Brazil (1). The intralesional infiltration technique was summarily described in almost all studies, limited to the interval between the infiltrations and the maximum number of applications. In the two publications from the Americas (Oliveira-Neto et al. 1997, Soto et al. 2013) anesthesia with lidocaine before the infiltration was recommend, unlike in the old-world studies. Although the expression "intradermal infiltration" was almost always used, only in one study (Shazad et al. 2005) the depth of the infiltration was detailed as "in the upper and mid dermis". Except for one author (Soto et al. 2013), who advocates the use of a fine-gauge needle (less than 25 gauge), all the others who mentioned the needle caliber (Oliveira-Neto et al. 1997, Firooz et al. 2005, Shazad et al. 2005, Khatami et al. 2013) have recommended needles between 30 and 40 gauge. No author mentioned the needle tilt; however, concerning the needle direction, four studies (Firooz et al. 2005, Khatami et al. 2013, Soto et al. 2013), described the procedure starting from the periphery to the centre of the lesion, moving the needle in all directions. Some authors recommended different volumes or doses of drug based on the area of the lesion (Firooz et al. 2010, Soto et al. 2013, Bumb et al. 2013), while others (Oliveira-Neto et al. 1997, Shazad et al. 2005, Khatami et al. 2013) proposed that the application should be of all the volume required to cause a visible change in the lesion ("saturation" or "blanching"), an aspect that is described as the desired outcome after infiltration in all studies. In turn, the direct monitoring of the infiltration procedure performed by a practitioner showed that the drug was injected only at the edges of the lesion. Thus, the following issues were considered unsolved:

(1) Should the intralesional approach be indicated for non-ulcerated lesions?

(2) How should the needle be directed during infiltration?

(3) What criteria must be observed for the definition of lesion saturation?

These remained conflicting or missing issues were submitted electronically to a panel of experts through objective questions - a methodology based on Delphi technique (Hsu & Sandford 2007). The approach includes several rounds of discussion to reach consensus. The experts were identified from the 10 research groups identified during the literature review. All of them were contacted for the resolution of unsolved issues, and only five of them responded to the questionnaire. All five experts considered intralesional therapy applicable to non-ulcerated lesions. Additionally, unanimously, all of them defined "saturation" as the presence of swelling. Three investigators indicated "elevation of the base of the lesion" as an observable manifestation for the understanding of the establishment of saturation, while two others defined saturation as "a disappearance of the gap between the centre and edge of the lesion". Only one consulted investigator considered the presence of pallor as an indispensable condition for achieving the saturation state. Based on that, the technique adopted was "to insert the needle toward the centre of the lesion and to move it back toward the edge while gently and continuously infiltrating the medication. The same movement is repeated in the radial direction until reaching the saturation of the full lesion: infiltration from each insertion point is directed in a V-shaped pattern towards the centre and the margin, together covering the bed of the entire lesion".

Finally, some definitions followed the usual understanding in elective skin surgical procedures (BAD 2014) namely, local cleaning with antiseptic solution prior to the procedure and buttons of anesthetics in the cardinal points adjacent to the lesion, preferably carried out with sterile gloves. Based on the knowledge of the skin layers, the recommendation to keep the needle in a parallel plane to the base of the lesion and with the bevel facing up to fill the dermis layer affected was also included in the SOP. So, it is possible to assume that the infiltration occurs deeply in the dermis and possibly in the adjunctive subcutaneous tissue. Considering the lack of available pharmacokinetic data for antimony administered by intradermal route, we opted for a more conser-

vative approach and limited the maximum daily dose to that recommended for parenteral use (three ampoules), according to the current recommendations (OPAS 2013). As in other skin procedures, the decision to use or not use a vasoconstrictor in association with lidocaine was left to the best medical understanding of the lesion site and the patient's characteristics. For the choice of the needle gauge we have adopted that one already used successfully in our service (25G x 0.7mm) into thread connection syringes. In the execution of the clinical study that supported the validation of intralesional infiltration SOP, the current recommendations for conducting CL clinical trials were followed, as proposed by Olliaro and collaborators in 2013, including the formula for calculating the area of the lesion, the definitions for the outcomes of interest and its moment of evaluation. Specifically, the lesion area was defined as the product of the two largest internal diameters of the ulcer (Olliaro et al. 2013).

The first step of validation, the content inspection, raised several ambiguities present in the first SOP version (script). As an example, the word "medication" was used to refer to both, 2% lidocaine and Glucantime®. Although a specialist can infer which exact medication was meant in each statement of the SOP, the word could cause misunderstandings in less attentive or less experienced physicians. The model analysis raised a question about possible different scenarios, such as different ulcer sizes and shapes. Even though a physician is supposed to identify and adjust the procedure accordingly, leaving these scenarios out of the scope of the SOP results in a variability in the application of the procedure, which goes against the proposed standardisation, so this too was modified in the following version.

Finally, the script was transformed into a more detailed tool encompassing a wider range of either small lesions, which require only an anesthetic point, or larger lesions requiring many anesthetic points to reach the entire extension of the lesion. In addition to that, an additional infiltration step, in the case of saturation not being achieved, was included in the script. This modified script was re-modeled and re-verified, which generated a few additional small issues. Thus, after four verification rounds, a more detailed SOP covering many possible scenarios that can be faced by the physician during the intervention was achieved (Fig. 2).

A total of 118 infiltrations were carried out over a 12-month period (August 2015 to July 2016) in 38 patients (the average of procedures per patient was three) after signing the consent form. Eighty-nine infiltrations were performed by three professionals with some previous experience in intralesional technique and 29 procedures were done by 14 physicians in training. The median total area of the lesions was 429 mm^2 and the median volume of Glucantime® administered on the first day of treatment was 5 mL (25-75% interquartile range 2.3 to 8mL).

The median procedure length was 12 min (ranging from 3 to 35 min), and in 72% of them, patients classified the pain during infiltration as mild (up to 3 in a visual analogue scale that goes from 0 to 10). The bleeding was also classified as mild (less than or equal to 3 on the modified Boezaart scale) in 96.6% of the procedures. Considering the items assessed by the checklist, full compliance with the SOP was observed in 66% of infiltrations. Despite this, in 100% of the inspected procedures, lesion saturation was observed at the end of infiltration. Instructions with a lower compliance rate were a needle tilt non-parallel to the base of the lesion during infiltration (20% of procedures), incomplete aspiration of the ampoule contents before starting the procedure (16% of procedures) and insertion of the needle into the lesion and not on intact skin (13% of procedures). Failure to comply with anesthesia procedures occurred in 12% of infiltrations. In all observed procedures, the recommended maximum limit of medication per day was observed. The professional's adherence to the SOP according to the previous experience was compared by univariate analysis to test the statistically stability (Table I). The Spearman correlation coefficient for professional's adherence to the SOP (experienced and not experienced medical doctors) is presented in Fig. 3. In this Figure, each point represents one of the criteria observed during the inspection of the procedures - detailed in Supplementary data, Figure

Material conditions
- 5-10 mL syringe filled with 2% lidocaine, coupled to insulin needle
- 5-10 mL syringe filled with Glucantime® coupled to 25 x 0.7G needle
- Sterile gloves
- Antiseptic and saline solution (to clean the lesion area)

Basic knowledge
- The maximum volume of Glucantime® allowed per day for patient is known
- Lesion saturation is the purpose of the procedure
- Saturation is defined as swelling of entire lesion

Technique

1. Perform the injection of lidocaine 2% using a 5 or 10 mL syringe coupled to insulin needle for the formation of many anesthetics buttons as many as deemed necessary according to the shape of the lesion. For a typical oval lesion it is suggested that the anesthetic buttons are located at the four cardinal points of lesion (as shown). The puncture occurs in healthy skin adjacent to the lesion, with 30º tilt;
2. Aspire entire Glucantime® ampoule contents using a 5 or 10 mL syringe coupled to a needle
3. Infiltrate Glucantime® using the following technique: insert the needle from anesthetic button toward the center of the lesion, tangential to its base and keeping the bevel faced up;
4. Move the needle back toward the edge of the lesion at the same time Glucantime® is gently infiltrated;
5. Repeat steps 2 and 3 in all anesthetic buttons;
6. Determine if there was saturation of the entire lesion, including the base / bottom and edges;
7. In the event of saturation of entire lesion, terminate the procedure and make the dressing;
8. In the event of non-satured areas in the lesion, proceed one or more new infiltration (s) from the nearest anesthetic bottom until saturation is obtained, considering the maximum dose of Glucantime® allowed per day

NOTE 1: If the volume required exceed 5 mL (1 ampoule), proceed again the complete aspiration of one Glucantime® ampoule contents as described in item 2

Fig. 2: final intralesional infiltration standard operational procedure (SOP) version.

TABLE I

Results of the procedure inspection according to professional experience

	Professionals without prior experience in therapy IL (Number of procedures: 29; number of professionals: 14)	Professionals with previous experience in therapy IL (Number of procedures: 89; number of professionals: 3)	p value
Time spent with the procedure in minutes (median, min-max)	13.5 (4-21)	12 (3-35)	0.21**
100% adhesion to the SOP	11/29 (38%)	67/89 (75%)	0.00*
Pain VAS scoring above 3	8/29 (28%)	25/89 (28%)	1*
Bleeding FBS scoring above 3	4/29 (14%)	35/89 (39%)	0,01*
Local anesthesia administration before infiltration	27/29 (93%)	77/89 (87%)	0.51*
Needle insertion from intact skin	26/29 (89%)	77/89 (87%)	1*
Complete ampoule contents aspiration before starting the infiltration	24/29 (83%)	75/89 (84%)	1*
Needle insertion from anesthetic button	27/29 (93%)	77/89 (87%)	0.51*
Needle position toward the center of the lesion	28/29 (97%)	85/89 (97%)	1*
Needle tilt parallel to the base of the lesion	18/29 (66%)	76/89 (85%)	0.02*
Placement of the bevel of the needle facing up	27/29 (97%)	89/89 (100%)	0.15*
Slow drug infiltration while rewinding the needle	26/29 (89%)	85/89 (96%)	0.36*
Understanding of the concept of saturation as swelling of the lesion	27/29 (93%)	89/89 (100%)	0.06*
Maximum drug limit per day was observed	29/29 (100%)	89/89 (100%)	-

FBS: modified Fromme-Boezaart scale; IL: intralesional; SOP: standard operational procedure; VAS: visual analogue scale; *: p value is computed using chi-square test; **: p value is computed using one-way ANOVA test.

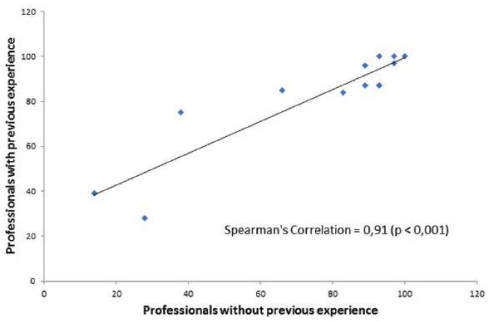

Fig. 3: the Spearman correlation coefficient for professional's adherence to the standard operational procedure (SOP).

(checklist) - and demonstrates the monotonic relationship between the paired data, in this case, the performance of the two groups of professionals, according to their previous experience. The parameters that differed between experienced and non-experienced medical doctors during the infiltration procedure execution were "*full adhesion to the SOP*", "*needle tilt parallel to the base of the lesion*" and "*bleeding scoring*". The last observation, the highest proportion of patients reporting bleeding with intensity greater than 3 during procedures performed by experienced medical doctors, was an unexpected result and required a logistic regression analysis to be analysed. All variables related to bleeding with a $p < 0.2$ in univariate analyses, namely "*needle insertion from intact skin*" ($p = 0.14$), *"needle tilt parallel to the base of the lesion"* ($p = 0.12$), "lesion area" ($p = 0.01$) were included in the initial model. The only factor related to bleeding intensity was the cutaneous lesion size (odds ratio 1.004, 95% confidence interval 1.000-1.004, $p = 0.01$).

Considering that there is no consensus on the requirement to perform local anesthesia prior to intralesional infiltration, we evaluated whether the intensity of pain reported by the patients was related to violation of the anesthesia procedures recommended in SOP (Table II). In the univariate analysis, only "*infiltration from non-intact skin*" was associated with the intensity of pain reported by the patients ($p = 0.03$).

To assess the changes in the outcomes of interest over time (Table III), we compared the first 45 infiltrations carried out during the validation study period performed by senior medical doctors (permanent staff) with the last 44 infiltrations carried out by these same professionals using statistical tests for paired samples. The percentage of compliance with the instructions increased and the score of pain reported by the patients reduced significantly over six months.

DISCUSSION

Evidence of validity and reliability are essential characteristics of evidence-based medicine, and the main consideration of a well-designed evaluation system is to ensure that the evaluation methods adopted are valid and reliable.

According to the 32nd Report produced by the WHO (WHO 1992), validation is "the documented act of prov-

TABLE II

The anesthetic recommendations adhesion during intralesional infiltrations grouped according to pain intensity referred by patients

	Pain VAS scoring until 3 (referred after 86 procedures)	Pain VAS scoring above 3 (referred after 32 procedures)	p value*
Local anesthesia administration not performed before infiltration	7/86 (8%)	7/32 (28%)	0.06
Needle insertion not performed from intact skin	7/86 (8%)	8/32 (25%)	0.03
Needle insertion not performed from anesthetic button	7/86 (8%)	7/32 (22%)	0.06

VAS: visual analogue scale; *: p value is computed using chi-square test.

TABLE III

Results of procedure inspection over time (procedures performed by professionals with previous experience with intralesional infiltration)

	The first 44 infiltrations performed by medical doctor seniors	The latest 45 infiltrations performed by medical doctor seniors	p value*
Time spent with the procedure in minutes (median, min-max)	11 (3-27)	12 (4-35)	0.11
Complete adhesion to the SOP	26/44 (59%)	41/45 (91%)	0.00
Pain referred by patient above 3 or mild pain	19/44 (43%)	6/45 (13%)	0.01
Bleeding FBS scoring above 3	22/44(50%)	13/45 (29%)	0.22

FBS: modified Fromme-Boezaart scale; SOP: standard operational procedure; *: p value is computed using McNemar test.

ing that any procedure, process, equipment, material, operation or system really leads to the expected results". There are several experiences in validating tools developed to assess psychomotor skills of medical trainees, allowing evaluation of competence (Beard et al. 2011, Raza et al. 2015). Although similar, in our case, the challenge was to validate a technical document with an instructive function (different from a "learning assessment method") and a medical process. As additional difficulties, the result of the process being evaluated is an outcome determined by multiple factors and therefore a result not easily measured. Besides that, a unique technique description for the process is not available; instead, significant differences are observed between the approaches undertaken by the various practitioners.

The content validation is an important step toward treatment guide standardisation, but it is still a manual and *ad hoc* process in the medical community and decisions concerning conflicting actions are taken based on intuitive aspects identified by the observers, based on prior knowledge and individual experience with the issue at hand. As in any document written in natural language, procedure guides are prone to errors and misunderstandings caused by ambiguities, omissions, or other inconsistencies that are difficult to detect in an informal revision. In addition, fault detection in the field incurs additional costs and re-work. Our results show that a formal SOP verification can pinpoint several issues early that would otherwise remain unknown and might compromise the applicability of this health tool. Specifically, *conflict analysis* tells us which actions in the SOP represent points of decision, where conditions and/or responses to the actions must be checked. By running this analysis, one is forced to check whether all possible alternatives/scenarios of the medical procedure are described or can be achieved somehow by following the script. The formal inspection guided by the computer also systematically identifies relationships between rules. This d*ependency analysis* is used to check whether the dependencies that are intuitively expected to occur are explicitly described. Finally, during the *rule sequence* analysis, it is possible to check whether the overall effect is the desired one and whether all possible outcomes are clearly considered and described in the script. Other issues raised are related to omission of information. In most cases, errors of omission occur because a certain tacit or technical knowledge is assumed in the document. Details of conflict, dependency and rule sequence analysis can be found in Cota et al. (2017).

For criterion validation, what we aimed was to assess the degree of consistency of outcomes between different performers and the SOP's adhesion rates. In the face of the lack of universal parameters that can be applied to all criterion validations, these parameters were anticipated as the main causes of variation in the intralesional infiltration procedure. Our analyses suggest that the proposed procedure is robust, which means that it tolerates some degree of modification in its execution, according to the

professional, without prejudice to the result. At the other hand, the increase in the adhesion rate to the instructions of the SOP reveals that the quality of the work of the professionals can improve over time. Although it has been demonstrated for experienced professionals in this study, this could possibly occur with any professional. In addition, the intralesional infiltration procedure proved to be a reproducible technique usable by professionals without previous training with high success and safety rates.

The low rate of a full adhesion to the SOP's instructions was mainly due to problems related to needle tilt during infiltration. It reflects a mechanical difficulty among less experienced professionals (an inability to perform the procedure as described in SOP) depending on the location, depth and size of the lesion. One possible explanation would be the fact that most of the invasive procedures performed on the skin by doctors using a needle are performed with a 30-degree inclination, such as local anesthesia and vascular puncture. On the other hand, even without fulfilment of the needle tilt recommendation, our results demonstrate that 100% of the procedures reached the desired result, i.e., the saturation of the lesion. This could mean that the needle tilt determined in SOP, a recommendation based only on the rational theoretical (to fill the skin layers known to be afflicted by the disease), would not be a requirement for the procedure. However, the implication of this technical detail on the cure rate has not been evaluated yet. Any therapeutic procedure ultimately should produce a cure or at least a favorable response with remission of the lesion. However, in this case, cure is not an immediate expected result after the procedure; there are many factors determining CL cure, including variables related to the parasite and the host, regardless of technical correction in any route of administration of the drug. Thus, by consulting experts, it was defined that the desired result of the intralesional infiltration procedure was the saturation of the lesion, defined as swelling of the entire lesion accompanied or not by pallor. Therefore, in addition to saturation achievement and considering the surgical nature of the approach, which could potentially produce pain, the patient's tolerance assessment system was also evaluated through a standardised pain scale, providing one more feasibility measure of the procedure. These findings suggest an association between pain intensity and some failure in the procedures recommended for local anesthesia.

The high percentage of cases achieving the desired outcome, the mild bleeding, the patients' high tolerance and the reliability presented in this study confirm that the procedure is feasible and is fit to be tested in future clinical trials addressing effectiveness. In short, the SOP presented here was developed taking account not only the Brazilian experience (Oliveira-Neto et al. 1997, Vasconcellos et al. 2012, Duque et al. 2016, da Silva et al. 2016) but also all the relevant aspects of the technique identified in the main experiences with this therapeutic procedure already reported. The SOP represents a useful tool to guide the MA intralesional infiltration for CL treatment within the good clinical practice principals, ensuring uniformity. In addition, the SOP was evaluated by accepted methods to guarantee clarify and correction, and after that, validated in relation to its robustness and reproducibility. All these aspects make this standardisation a useful instrument for the effective incorporation of the antimoniate meglumine intralesional infiltration approach, as recently proposed by the Ministry of Health in Brazil (MS 2017).

AUTHORS' CONTRIBUTION

RES, GFC, EFC conceived the study; GFC, RES, DBR, MCS, HSAM designed the study protocol and carried out the clinical assessment; GFC, RES and EFC conducted the analysis and interpretation of these data; EFC carried out the formal inspection; GFC, RES and JPC drafted the manuscript; AR critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

The Authors declare that there is no conflict of interest. All relevant data related to this manuscript are available without restrictions.

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6 CONSIDERAÇÕES FINAIS E CONCLUSÃO

A ideia de que apenas a experiência leva a uma prática correta pode ser enganosa. A experiência é vital, mas sem algum controle pode levar a perpetuação de uma prática errada. Em todas as áreas que buscam a qualidade, sistemas de avaliação precisam ser desenvolvidos para assumir um papel regulador, assegurando a qualidade da prática, e no caso da saúde, proporcionando segurança do paciente. A principal consideração de um sistema de avaliação bem concebido é garantir que os métodos de avaliação adotados são válidos e confiáveis. Evidências de validade e confiabilidade são características essenciais do cuidado baseado em evidências e um pré-requisito para a incorporação de tecnologias nos serviços de saúde, seja geridos com os recursos públicos ou privados.

Estudos de validação, de modo geral, têm por objetivo avaliar se determinado processo consegue gerar produtos conformes. Resumidamente, a metodologia consiste em obter uma amostra de produtos fabricados em condições normais de operação, avaliar a estabilidade estatística (ou previsibilidade) do processo e, determinar a capacidade deste processo gerar produtos dentro das especificações. No caso de processos na área da saúde, considerando a inexistência de um "produto-objeto", o desafio da validação é ainda maior. A padronização de um roteiro-guia para a infiltração intralesional de antimoniato de meglumina impôs desafios adicionais, o primeiro, a dificuldade de se mensurar o resultado desejado; o segundo, a falta de uniformidade na execução de um procedimento já incorporado na prática assistencial. Apesar de conter muitas especificidades, optou-se pela aplicação da metodologia de validação baseada na psicometria, pelo reconhecimento da natureza humana do processo em questão, associada a métodos bem descritos de validação já aplicados na avaliação de qualidade em indústria de artigos críticos, tais como a farmacêutica e de softwares.

A validade de conteúdo refere-se ao julgamento sobre a qualidade da descrição do instrumento, ou seja, se ele realmente abrange todas as ações incluídas no procedimento proposto e se não contém elementos (ou ações) que pode ser atribuído a outros procedimentos. Classicamente a validade de conteúdo não é determinado estatisticamente, mas realizada por pares e consite na leitura dos diferentes examinadores peritos, que avaliam a representatividade dos itens em

relação a áreas de conteúdo e relevância dos objetivos a serem alcançados. Os procedimentos metodológicos para a validação de conteúdo começam com a construção do instrumento. Apesar de seguir uma metodologia definida, os exemplos de validação de conteúdo para instrumentos na área da saúde são baseados em um processo informal, onde as decisões para ações conflitantes são tomadas com base em aspectos intuitivamente identificadas pelos observadores, com base no seu conhecimento prévio e experiência individual com o assunto em questão.

Embora a experiência prévia dos profissionais atuantes no CRL com a abordagem intralesional tenha contribuido para a elaboração preliminar do guia para o procedimento, a proposta neste estudo foi investigar, comparar e incluir descrições técnicas usadas por outros profissionais e já publicadas. Adicionalmente, optou-se por analisar sob o ponto de vista estrutural o instrumento, inclusive sob a perspectiva de indivíduos não afeitos ao tema, para checar sua auto-suficiência em transmitir uma informação. Nossas análises confirmam que a inspecção formal complementa a avaliação intuitiva por pares e pode otimizar processos, contribuindo para a redução de falhas.

Para a validação de critério, essencialmente o que se busca é avaliar o grau de concordância de desfechos entre diferentes executores e para o mesmo executor ao longo do tempo, para identificar quais variáveis e o quanto sua variação influenciam o desfecho pretendido. Neste sentido, nossas análises sugerem que o procedimento proposto de infiltração intralesional de antimoniato de meglumina é robusto e reprodutível, podendo ser utilizado por profissionais sem treinamento prévio, de forma segura e bem tolerado pelos pacientes.

A análise de construto é a mais difícil de obter. Tratando-se de um procedimento terapêutico, em última análise, o que se deseja produzir é uma resposta clínica favorável que se traduz em remissão da lesão. Entretanto, além de tratar-se de um resultado não imediato (o que não ocorre imediatamente após o procedimento, mas sim ao longo de semanas), são inúmeros os fatores determinantes do desfecho cura, incluindo variáveis relacionadas ao parasita e ao hospedeiro, independentemente da correção da técnica em qualquer via de administração do medicamento. Assim, a revisão da literatura realizada e a consulta eletrônica ao grupo de especialistas foram unânimes em indicar que o resultado almejado para o procedimento de infiltração intralesional era a saturação da lesão, definida como seu intumescimento de fundo e bordas, acompanhado ou não por

palidez. Idealmente a validade de construto deve ser demonstrada por uma acumulação de provas. Por isso, além da observação da saturação, considerando tratar-se de procedimento passível de causar sangramento e dor, o que poderia inviabilizar sua execução, incluiu-se ainda a tolerância do paciente, avaliada por escala padronizada de dor, além de avaliação de intensidade de sangramento, como uma medidas a serem consideradas na definição de exequibilidade do processo, medida importante de validação. O pequeno volume de sangramento e a boa tolerância do paciente confirmaram que o procedimento é exequível, estando apto para futuras provas de eficácia.

A principal limitação deste estudo é sua baixa validade externa, considerando que todos os procedimentos de infiltração intralesional foram realizados em um único centro, referência para tratamento de leishmaniose, em condições estruturais adequadas e sob a supervisão de uma enfermeira-pesquisadora. Novos estudos em diferentes cenários de atendimento a pacientes com LC distribuídos nas várias regiões brasileiras deveriam ser conduzidos a fim de confirmar nossos resultados. Da mesma forma, outras medidas podem ser propostas como parâmetros a serem avaliados na validação de critério, construto e conteúdo. Da mesma forma, este estudo não exclui a existência de outras técnicas de infiltração intralesional de antimoniato de meglumina igualmente reprodutíveis e eficazes na produção de saturação da lesão. Variações nas ações propostas no POP podem ser tentadas, com análise do impacto gerado no resultado saturação, sangramento e tolerância do paciente, como por exemplo, a realização do procedimento sem a infiltração prévia de anestésico, como proposto por alguns autores.

A contribuição deste trabalho foi à confirmação da viabilidade de padronização de um procedimento de infiltração intralesional de antimoniato de meglumina, passível de ser executado por profissionais sem treinamento prévio, de forma reprodutível e segura. Considerando que a abordagem foi recentemente incorporada entre as opções terapêuticas recomendadas para LC no Brasil, O POP pode ser ferramenta útil no treinamento de profissionais médicos a serem iniciados na execução do procedimento. Por fim, a utilização em larga escala de método padronizado de infiltração deve permitir a reunião da evidência de eficácia e segurança com a abordagem intralesional, subsidiando o manejo da LT.

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