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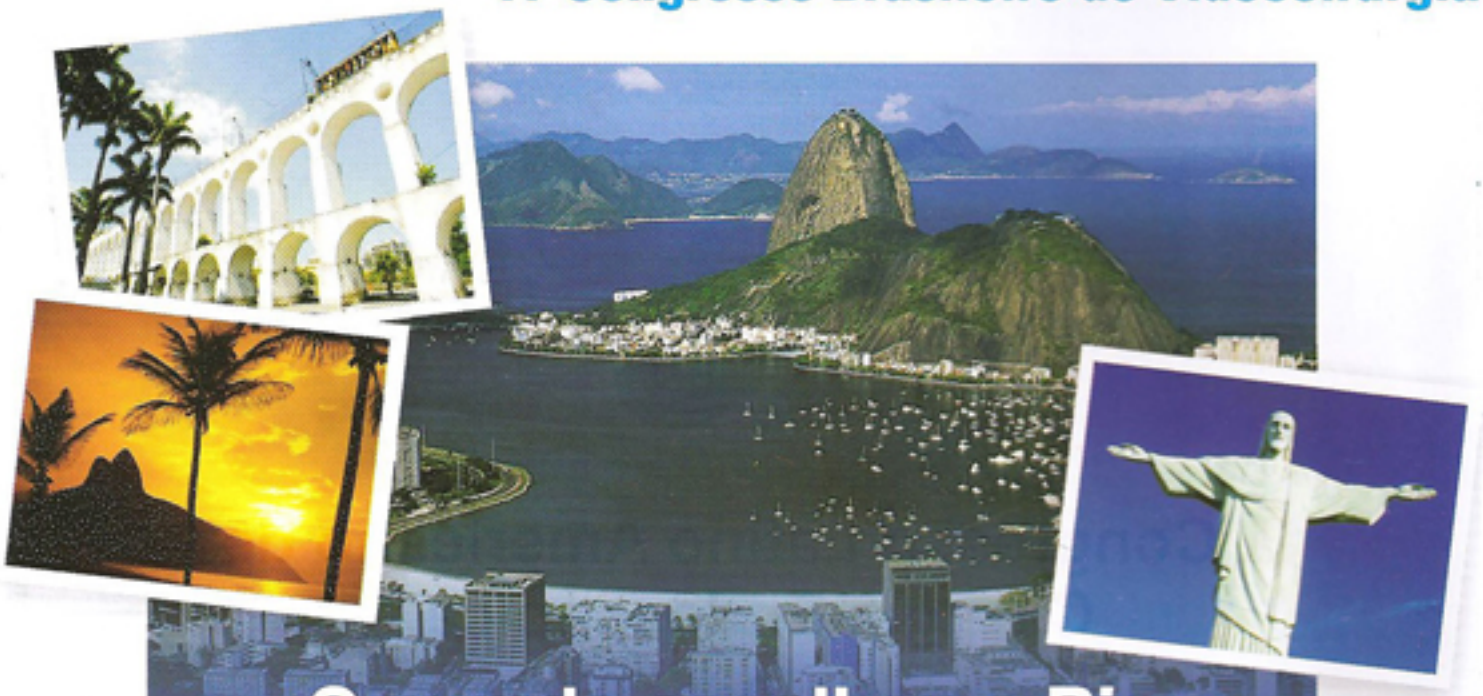

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Brazilian Journal of Videoendoscopic Surgery

Editorial

Understanding Randomized Controlled Trials

Entendendo Ensaios Clínicos Randomizados

MARCO AURÉLIO PINHO DE OLIVEIRA[1]; RAPHAEL CÂMARA MEDEIROS PARENTE[2]

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Clinical trials constitute a powerful tool for evaluating health interventions, be they medication interventions or not.[1] The first clinical trial, similar to the design we know today, was published in the late 1940s,[2] when the statistician Sir Austin Bradford Hill randomly assigned patients with pulmonary tuberculosis into two groups: those who would receive streptomycin and those who would not receive the medication. In this way Hill was able to evaluate, in an unbiased fashion, the efficacy of streptomycin. Despite the increasing publication of controlled clinical trials, some aspects of the design and the analysis are still misunderstood and misinterpreted.

Clinical trials are studies in which one group receives a treatment or exposure and is accompanied and compared with a control group. Unlike observational studies in which the researcher does not interfere in the exposure, in clinical trials the researcher plans and actively intervenes in the factors that affect the sample, thus minimizing the influence of confounding factors. The allocation or assignment of research subjects may be random or nonrandom.

Although randomized controlled trials (RCTs) are the gold standard for determining the effect of a therapy, for various reasons its use in surgery is not as widespread as in other medical specialties.[3] Clinical trials are laborious and costly to carry out, and the development and execution of clinical trials of surgical interventions poses additional methodologic and practical challenges.

Randomized comparisons of surgical interventions have been carried out many years. Various surgical interventions used for long periods of time were found to be ineffective and were abandoned after they were subjected to this kind of study.[4] The ligature of the internal mammary artery was abandoned after two small clinical trials found no difference in relation to placebo. More surprising, the number of clinical trials in surgery has not accompanied that of other specialties.

A review found a marked increase in the number of randomized clinical trials from 1990 to 2000.[5] And yet only 3.4% of all articles published by important surgical journals were clinical trials.[6] The contrast with other clinical areas can be seen by comparisons of audits of databases for clinical practice in internal medicine and various surgical specialties. Whereas half of interventions in internal medicine are based on evidence from clinical trials, two surgical audits reported that fewer than one quarter of surgical interventions have comparable evidence.[6-7]

The main problem associated with clinical trials in surgery – and which impedes their design and execution – is the difficulty in blinding. Masking is the process of retention of information about the interventions received by each group is a key element in the design of RCTs. When done successfully, it is viewed as having an important role in preventing the introduction of an information bias. Blinding can be applied to the study subjects, to the researchers, and even to the statisticians calculating the results of the study. In clinical trials of surgical interventions, blinding poses a much greater challenge than in trials of pharmaceutical interventions. It is impossible to bar a surgeon from knowing what technique he will be using. Thus, it is impossible to blind the surgeon. But blinding generally does not occur in surgical interventions even for the study participants. This happens because of the routine practice of the patient returning to the

surgeon who operated post-operatively for follow-up. The blinding of patients is feasible when the same surgical access is used for different surgical procedures. Blinding patients is more difficult when the surgical approaches are different, for example, laparotomy compared with laparoscopy, and it is virtually impossible when one compares surgery with medical management. Although surgery as a placebo is theoretically possible – and there are examples in the literature[8] – the conception of such studies is often impeded by ethical considerations.

Carefully conducted randomized clinical trials are the gold standard among studies to guide our day-to-day clinical practice. In developing a RCT one seeks a study that is large enough that an important clinical effect can achieve statistical significance, but not so big that minor outcomes are significant.

Moreover, when excessively large, RCTs can be prohibitively expensive.[9] The sample size for any study is calculated based on the number of type I and II errors that the researcher is willing to tolerate. A strength of RCTs is that random assignment minimizes the impact of confounding factors by distributing them equally among the groups. However, there are major drawbacks of a single large RCT.

First, some RCTs are so methodologically rigorous that findings are only applicable to the population studied (problems of external validity or generalizability). In addition, patients participating in clinical trials may have a baseline risk for the outcome of interest that is much greater than the average of the patients of the population or the subjects may be from very different populations. For example, some studies that have investigated calcium intake for the prevention of pre-eclampsia have been carried out in countries with very different diets, which makes it difficult to extend conclusions to populations with other diets. This can limit the generalizability of findings. Another issue is that some clinical trials may not have a sufficient number of individuals in important subgroups.

A final concern with randomized controlled trials is the issue of publication bias. Publication bias occurs when the findings of studies that report positive results (i.e, statistically significant) are more likely to be published than studies with negative results. The studies that report significant results may result in a greater number of publications and will also be published in journals of greater impact. In this way publication biases may affect meta-analysis since these are unable to consider trials with unfavorable findings that were never published.

A randomized clinical trial is a prospective study of human subjects comparing the effect and value of an intervention versus a control.[10]

1. Randomized controlled trials should be considered when:

a. There is uncertainty about the effect of an exposure or treatment;

b. The exposure can be changed in the study.

2. Potential limitations of randomized clinical trials include:

a. Limited generalizability of the study population.

b. Limited generalizability of the environment under study.

c. Randomized clinical trials address a specific study question.

3. The usual measures of the magnitude of effect in randomized clinical trials are relative risk and risk difference.

In RCTs, a treatment or procedure may be compared to no treatment, treatment with a similar medication (e.g., same class of drugs in head-to-head trials), with a placebo, or a preexisting standard of care.[10] RCTs are conducted under controlled conditions to ensure that the study hypothesis is tested in a reproducible manner. RCT protocols often cannot be repeated in clinical practice. The highly specialized conditions in which in a randomized trial is conducted may result in conclusions that are internally valid, but which cannot be generalized to patients with the same disease outside the study.[10]

4. Randomized clinical trials are designed to definitively answer a specific question, focusing strictly on a research hypothesis, isolating the effect of one or a small number of therapies. Randomized clinical trials are not designed to evaluate the mechanisms by which a therapy can produce benefits or harm. They usually have narrow clinical applicability. The conclusions derived from RCTs are limited to the situations in which the exposure of interest can be modified in a study environment, for example, using medications or lifestyle changes. There are innumerable exposures that are extremely worthy of investigation, but which cannot be easily modified, such

as genes, serum markers, socioeconomic conditions, etc.

Randomized controlled trials are limited to specific clinical situations in which the exposure of interest can be easily modified. Nor can they be used in situations where exposure is known to be deleterious, because it is not ethical. For example, we cannot get someone to smoke in order to be compared with a group who do not smoke because we already know hazards of smoking.

The investigation of new drugs by the pharmaceutical industry involves RCTs in different phases. They are carried out in basically four phases[10]:

Phase I Studies

The first step in developing a new drug is to understand whether the medication is well tolerated in a small number of people. Although not controlled clinical trials, these types of studies are referred to as Phase I studies. Participants in Phase I trials are either healthy adults or people with the specific disease that the drug is intended to treat. Occasionally, phase I studies cannot be performed in healthy adults because the drug has unacceptable adverse effects; this is the case with chemotherapeutic agents. Phase I trials seek to determine what maximum dose a drug can be administered before unacceptable toxicity occurs. These studies are begin with low doses in a limited number of people, with the dose increased gradually.

Phase II Studies

Phase II studies are designed to evaluate whether a drug has biological activity and to determine its safety and tolerability.

Phase III / IV Studies

Phase III studies are randomized clinical trials designed to assess the efficacy and safety of an intervention. The results of phase III studies are clinical endpoints such as death or tumor-free survival. Assessments of safety occur over a longer period than with phase II studies. Phase IV studies occur after regulatory approval and measure outcomes associated with a drug or intervention in routine clinical use in the general population.

In the critical evaluation of a randomized clinical trial, we should ask several important questions, using some information already outlined above.

The first question one should ask is "Are the patients selected for this study similar to patients that I treat?"

The study should state clearly the inclusion and exclusion criteria (e.g. age, gender, prior illnesses, etc.) The conclusions of studies with very restrictive inclusion criteria are limited in terms of their generalizability (but are more specific).

The study report should also mention how patients were selected from the general population. Several examples that might introduce biases: Were study enrollees all patients who presented to a tertiary hospital? Were they paid volunteers, and if so, were they patients drawn from a poor community near the hospital?

Remember that we can only generalize to populations similar to the one in the study. It is up to the reader to decide whether differences between the population selected in the study and the population that interests them are important or not.

Another key aspect is the clinical endpoint of interest. Many studies that are well structured methodologically, but evaluate variables that are not very useful clinically, or do not represent what they should. For example, in the treatment of endometriosis with an antiestrogen drug, the researcher finds only a statistically significant decrease in the American Fertility Society (AFS) score – which quantifies the extent of disease – and concludes that treatment is effective. But what endometriosis causes is basically infertility and pelvic pain, and the study in question did not assess what really matters (the clinical endpoint of interest), that is, if the patient's pain improved or that she was able to get pregnant (the patient is not interested only in improving their AFS score). Another example would be a study to evaluate the effectiveness of a new chemotherapeutic agent, using as parameter only the reduction of tumor mass. The decrease of the tumor, however, may not correlate with survival, which is the outcome variable of interest for the patient.

Another important issue is how individuals were allocated between the treatment group and control (or placebo) group. Studies that do not include a control or placebo group run the risk of showing that a treatment is effective when in fact it is not. A "placebo effect" can even produce improvement in symptoms in more than 50% of subjects. The placebo may even be more effective that the medication being studied! In other words, a patient's improvement might

occur not because of the treatment in question, but for other reasons: the natural history of the disease process, psychological aspects, etc. Sometimes, as for example, in the treatment of acute pelvic inflammatory disease, it is inappropriate to use of a placebo or have no treatment as the control. In these cases, the investigator can study a new drug using as a control group the treatment considered the standard of care.

The next step is to verify how the randomization was done between the treatment and control groups. Randomization implies the chance assignment of patients so that each case has the same probability of being allocated to the intervention or control group. Non-randomized controlled studies are viewed as not have the same weight of scientific evidence as RCTs, because in most cases the intervention and control groups are not equivalent (i.e., there is some bias). For example, in a study comparing Laparoscopic Burch Urethropexy and laparotomy, one could imagine that patients who were thinner and who had milder complaints of stress urinary incontinence might be selected for laparoscopy. If this selection bias were to occur, one could not compare these two distinct groups of patients, as it would put laparotomy at a disadvantage.

Randomization ends up balancing known factors such as age, weight, stage of illness, as well as unknown (or immeasurable) factors (e.g., some genetic factor that cannot readily be detected that might influence the clinical outcome). True randomization should be done with random numbers generated by computer (there are also tables for this purpose) that are placed in numbered sealed envelopes that are opened immediately before treatment is administered. Inappropriate methods of randomization – sometimes called "quasi-randomized" – include, for example, doing laparoscopic surgery on Mondays and Wednesdays and laparotomies on Tuesday and Thursday, or alternating laparoscopic surgery and laparotomy. These methods permit failures in the random assignment, even if unconsciously. For example, the surgeon (or the physician who referred the patient for surgery and is familiar with the design of the study) may consider a patient too obese for laparoscopy and subconsciously (or intentionally) postpone the surgery for a day, in order to coincide with day or turn for a laparotomy. Appropriate randomization will generally prevent this type of bias. Nevertheless, well executed randomization does not guarantee the equivalence of the groups, especially with small samples. Before analyzing the data, it is good idea to check if there really was a balanced assignment of patients, particularly regarding those characteristics which directly influence the outcome, such as disease stage, age, weight, etc.). Unbalanced groups may bias the results.

One should also be concerned if the method used in measuring the clinical endpoint of interest was double-blinded. This means that neither the patient nor the professional making the assessment (for example, assessing the degree of postoperative pain in patients who may or may not have received the anesthetic marcaine in a surgical wound) may know whether the treatment was applied. The physician may unconsciously not fully appreciate the complaints of patients who belong to the group that received the investigational treatment, distorting the results. The patient may want to believe in a particular investigational or novel treatment and thus downplay or underreport symptoms. The double-blind method attempts to eliminate this potential type of subliminal bias. As with comparisons of clinical and surgical treatments, a double-blind approach is not always feasible. But you should not neglect to use a double blind approach whenever possible.

Another important aspect is the duration of follow-up. First make sure that the duration of follow-up was adequate to assess the clinical outcome of interest. For example, in assessing the use of laparoscopic transection of the utero-sacral ligaments for relief of dysmenorrhea, the duration of follow-up should be at least one year, as the high number of relapses after this period is well established. Another relevant issue is whether the percentage of patients who were lost to follow-up was similar among the groups. Follow-up rates below 70% make it virtually impossible to analyze the data, as the abandonment may have occurred because of side effects or even deaths stemming from the treatment.

The aforementioned errors are systematic, as opposed to random errors that can occur when working with any sample. The appropriate statistical analysis aims to identify whether the differences in results were obtained due to random errors or if a difference really does exist between the intervention and the control. The basic concepts of statistics will be addressed in the next issue of this journal.

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Brazilian Journal of Videoendoscopic Surgery

Editorial

Entendendo Ensaios Clínicos Randomizados

Understanding Randomized Controlled Trials

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Os ensaios clínicos constituem-se numa poderosa ferramenta para a avaliação de intervenções para a saúde, sejam elas medicamentosas ou não[1]. O primeiro ensaio clínico, nos moldes que hoje conhecemos, foi publicado no final da década de 40[2], quando o estatístico Sir Austin Bradford Hill alocou aleatoriamente pacientes com tuberculose pulmonar em dois grupos: os que receberiam estreptomicina e os que não receberiam o medicamento. Desta forma, ele pode avaliar, de maneira não viesada, a eficácia deste medicamento. Em que pese a publicação crescente de ensaios clínicos controlados, alguns aspectos do desenho e da análise ainda são mal compreendidos e interpretados de forma equivocada.

Os ensaios clínicos são estudos onde um grupo de interesse em que se faz uso de uma terapia ou exposição é acompanhado comparando-se com um grupo controle. Diferente dos estudos observacionais em que o pesquisador não interfere na exposição, nesse estudo o pesquisador planeja e intervém ativamente nos fatores que influenciam a amostra, minimizando assim a influência dos fatores de confundimento. A alocação dos sujeitos de pesquisa pode ser de forma aleatória (randomizada) ou não-aleatória.

Embora os ensaios clínicos randomizados (ECRs) sejam o padrão-ouro para determinação de efeito de uma terapêutica, por diversos motivos, seu uso na cirurgia não é tão difundido como nas outras especialidades médicas[3]. Ensaios clínicos são laboriosos e custosos em realizá-los e na cirurgia trazem consigo diversos desafios práticos e metodológicos na sua elaboração e realização.

As comparações randomizadas de intervenções cirúrgicas têm sido realizadas por muitos anos. Várias intervenções cirúrgicas usadas por períodos longo de tempo têm-se mostrado ineficazes e depois descartadas após submetidas a esses estudos[4]. A ligadura da artéria mamária interna foi descartada após resultados de dois pequenos ensaios clínicos não terem demonstrado diferença em relação ao placebo. Mas surpreendentemente, o número de ensaios clínicos na cirurgia não acompanha o de outras especialidades.

Uma revisão encontrou um aumento no número de ensaios clínicos randomizados de 1990 a 2000[5]. No entanto, apenas 3,4% do total de artigos em importantes revistas cirúrgicas foram ensaios clínicos[6]. O contraste com outras áreas podem ser vistas por comparações entre auditorias de bases de dados para a prática clínica em medicina interna e diversas especialidades cirúrgicas. Considerando que metade das intervenções em medicina interna foram julgadas com base em evidências de ensaios clínicos, duas auditorias cirúrgicas relataram um quarto ou menos quando avaliadas evidências cirúrgicas[6-7].

O principal problema relacionado aos ensaios clínicos na cirurgia e que dificultam sua confecção e realização é a dificuldade no mascaramento. O mascaramento é o processo de retenção da informação sobre as intervenções atribuídas a cada grupo e é um elemento-chave na concepção de ECRs. Quando feito com sucesso, é reconhecido como tendo um papel importante na prevenção da introdução de um viés de informação. O cegamento pode ser aplicado aos participantes, aos pesquisadores e aos avaliadores dos resultados do estudo. Em ensaios clínicos cirúrgicos, o mascaramento coloca um desafio maior do que para terapias medicamentosas. É impossível impedir que o cirurgião saiba qual técnica ele estará usando. Logo, é impossível o mascaramento do médico. Os avaliadores podem, e devem, preferencialmente, ser mas-

carados quanto aos resultados. No entanto, o mascaramento não ocorre geralmente em intervenções cirúrgicas para nenhum dos participantes do estudo. Isso ocorre devido ao hábito do paciente retornar ao médico que o operou para o seguimento. O mascaramento dos pacientes pode ser conseguido quando se usa a mesma via para cirurgias diferentes. O mesmo é mais difícil de se obter quando as vias são diferentes como por exemplo laparotômica comparada com laparoscópica e virtualmente impossível quando se compara cirirgia com medicamentos. Embora cirurgia como placebo seja teoricamente possível, motivos éticos impedem sua concepção na prática, embora haja relatos na literatura[8].

Ensaios clínicos bem conduzidos são o padrão-ouro entre os estudos para guiarem a nossa prática clínica diária. A elaboração de um ECR visa a um estudo que seja suficientemente grande para que um efeito clínico importante seja estatisticamente significativo, mas não tão grande para que desfechos pouco importantes sejam significativos. Além disso, quando excessivamente grandes, os ECRs podem ser proibitivamente caros[9]. O tamanho da amostra para qualquer estudo é calculado com base na quantidade dos erros tipo I e II que o investigador está disposto a tolerar. Um ponto forte dos ECRs é que a alocação aleatória evita o fator de confundimento por dispersar igualmente esses fatores entre os grupos de forma paritária. No entanto, existem importantes inconvenientes de um único ECR de grande porte. Primeiro, alguns ECRs são tão rigorosos na sua metodologia que os resultados podem somente servir para essa população estudada (problemas de validade externa ou de generalização). Além disso, os pacientes que participam de ensaios clínicos podem ter uma linha de base de risco para o desfecho de interesse muito maior do que a média dos pacientes da população ou podem ser oriundos de populações muito diferentes. Por exemplo, alguns dos estudos que estudaram a ingesta de cálcio para a prevenção da pré-eclâmpsia (embora com metodologia rigorosa) foram realizados em países com dietas muito diferentes entre si o que impede conclusões para populações com dietas outras. Isso pode impedir uma generalização dos resultados.

Além disso, alguns ensaios clínicos podem não possuir um número suficiente de indivíduos em subgrupos importantes. Uma preocupação final com o ECR é a questão do viés de publicação. O viés de publicação ocorre quando os resultados dos estudos que relatam resultados positivos (com significância estatística) são mais prováveis de serem publicados do que estudos com resultados negativos. Os estudos que relatam resultados significativos podem resultar em um maior número de publicações e também poderão ser publicados em jornais de maior impacto. Isso pode ter impacto na confecção de metanálises que podem não englobar ensaios com resultados desfavoráveis.

Um ensaio clínico randomizado é um estudo prospectivo em humanos comparando o efeito e o valor de uma intervenção contra um controle[10].

1. Ensaios clínicos randomizados devem ser considerados quando:

a. Há incerteza sobre o efeito de uma exposição ou tratamento;

b. A exposição pode ser modificada no estudo.

2. Potenciais limitações de ensaios clínicos randomizados incluem:

a. Limitada generalização da população em estudo.

b. Limitada generalização do ambiente em estudo.

c. Ensaios clínicos randomizados respondem a uma questão de estudo específica.

3. As medidas de magnitude de efeito usuais em ensaios clínicos randomizados são o risco relativo e a diferença de risco.

Em ECRs, um tratamento ou procedimento pode ser comparado a nenhum tratamento, a uma terapêutica semelhante (mesma classe de drogas nos *head-to-head trials*), com um placebo ou a uma norma preexistente de acompanhamento[10]. ECRs são realizados sob condições controladas para garantir que a hipótese do estudo é testada de uma forma reprodutível. Protocolos de ensaios clínicos randomizados muitas vezes não podem ser repetidos na prática clínica. O ambiente de estudo especializado de um estudo randomizado pode resultar em conclusões válidas internamente, mas os resultados não podem ser generalizados para pacientes com a mesma condição fora do estudo[10].

4. Ensaios clínicos randomizados são projetados para responder definitivamente uma questão específica, concentrando-se estritamente em uma hipótese de pesquisa, isolando o efeito de uma ou de

um pequeno número de terapias. Ensaios clínicos randomizados não são projetados para avaliar os mecanismos pelos quais uma terapia pode produzir benefícios ou prejuízos.

Costumam ter uma aplicabilidade clínica limitada. Conclusões retiradas de ECRs são limitadas a situações em que a exposição de interesse pode ser modificada em um ambiente de estudo, por exemplo, uso de medicamentos ou mudanças de estilo de vida. Há inúmeras exposições que são altamente relevantes para estudo, mas não podem ser facilmente modificadas, tais como genes, marcadores séricos, condições socioeconômicas etc.. Ensaios clínicos randomizados são limitados a situações clínicas específicas nas quais a exposição de interesse pode ser facilmente modificada. Também não podem ser usados em situações nas quais a exposição seja reconhecidamente deletéria, por não ser ético. Por exemplo, não podemos fazer com que alguém fume para compararmos com um grupo que não fume por já sabermos dos malefícios do fumo.

A pesquisa de drogas pela indústria envolve ECRs nas suas diferentes fases. São realizadas basicamente em 4 fases[10]:

Estudos Fase I

O primeiro passo no desenvolvimento de uma nova droga é entender se o medicamento é bem tolerado em um pequeno número de pessoas. Embora não seja um ensaio clínico, estes tipos de estudos são referidos como estudos de fase I. Os participantes de estudos de fase I são adultos saudáveis ou pessoas com a doença específica que a droga se destina a tratar. Ocasionalmente, estudos de fase I não podem ser realizados em adultos saudáveis porque a droga tem inaceitáveis efeitos adversos, tais como agentes quimioterápicos. Estudos de fase I procuram determinar até que dose uma droga pode ser administrada antes de ocorrer toxicidade inaceitável. Esses estudos são iniciados com baixas doses em número limitado de pessoas e, em seguida, aumenta-se a dose gradualmente.

Estudos de Fase II

São projetados para avaliar se um medicamento possui atividade biológica e para determinar sua segurança e tolerabilidade.

Estudos de Fase III / IV

Os estudos de fase III são ensaios clínicos randomizados delineados para avaliar a eficácia e a segurança de uma intervenção. Os resultados dos estudos de fase III são desfechos clínicos, tais como morte ou sobrevida livre de tumor. As avaliações de segurança ocorrem durante um período mais longo quando comparados com estudos de fase II. Estudos de fase IV ocorrem após aprovação e avaliam os resultados associados a uma droga ou intervenção na prática clínica com o uso na população geral.

Na avaliação crítica de um ensaio clínico randomizado, devemos fazer algumas perguntas importantes, usando algumas informações já assinaladas anteriormente.

A primeira pergunta que se deve fazer é "Os pacientes selecionados neste estudo são semelhantes aos pacientes que eu trato?". O trabalho deve dizer claramente quais foram os critérios de inclusão e exclusão (idade, sexo, doenças anteriores, etc..). Trabalhos com critérios muito rígidos de inclusão são mais restritivos na generalização das conclusões (porém são mais específicos). Deve mencionar ainda como os pacientes foram selecionados da população geral (Só entraram os pacientes que procuraram o hospital terciário? São apenas voluntários remunerados? ou são apenas os pacientes de uma comunidade carente próxima ao hospital?). Lembrar que só podemos generalizar para as populações semelhantes ao do estudo em questão. Cabe ao leitor decidir se as diferenças entre a população selecionada no estudo e a população que lhe interessa são importantes ou não.

Um dos aspectos fundamentais é o evento final de interesse. Muitos trabalhos são até metodologicamente bem montados, porém estudam variáveis que não são muito úteis clinicamente, ou que não representam aquilo que deveriam. Por exemplo, no tratamento da endometriose com uma medicação antiestrogênica, o pesquisador verifica somente uma diminuição estatisticamente significativa do score da AFS (quantifica a extensão da doença) e conclui que o tratamento é eficaz. Porém, o que a endometriose causa é basicamente infertilidade e dor pélvica, e o estudo em questão não avaliou o que realmente interessa (evento final de interesse), ou seja, se a paciente melhorou da dor ou se conseguiu engravidar (não interessa à paciente melhorar somente o score da AFS). Outro exemplo seria uma pesquisa para verificar a eficácia de um novo quimioterápico, tendo como parâmetro apenas a diminuição da massa tumoral (porém, a diminuição do tumor pode não se correlacionar com a sobrevida, variável de interesse para a paciente).

Outro aspecto importante é saber como foi feita a distribuição dos indivíduos entre o grupo tratamento e o grupo controle (ou placebo). Trabalhos que não incluem grupo controle ou placebo perdem muito (correm o risco de mostrar que um tratamento é eficaz quando na verdade não é), pois o placebo pode produzir efeitos (p.ex. melhora da cefaléia) superiores a 50% (pode inclusive ser melhor que o medicamento estudado!), ou seja, a melhora do paciente pode acontecer não pelo tratamento em questão, mas sim por outros motivos (história natural da doença, aspectos psicológicos etc.). Algumas vezes a utilização de um placebo (não tratamento) é inadequado, como por exemplo no tratamento de uma doença inflamatória pélvica aguda. Nestes casos, o pesquisador pode comparar um novo medicamento usando como grupo controle o tratamento considerado padrão .

O próximo passo a ser verificado é saber como foi feita a randomização entre os grupos tratamento e controle. A randomização implica na distribuição aleatória dos pacientes, de modo que cada caso possa ter a mesma chance de ser alocado nos diferentes grupos. Estudos controlados (i.e., com grupo controle) não randomizados perdem na qualidade da evidência científica, pois na maioria das vezes os grupos não são homogêneos (grupos viciados). Por exemplo, num estudo comparativo entre a cirurgia de Burch laparoscópica *versus* laparotômica, pode ser que sejam selecionadas para a laparoscopia pacientes mais magras e com queixas mais leves de incontinência urinária de esforço. Deste modo, não se pode comparar estes dois diferentes grupos de pacientes (neste caso desfavorece a cirurgia por laparotomia). A randomização acaba ajustando esses fatores conhecidos (idade, peso, grau da doença etc.) assim com fatores desconhecidos (p.ex. algum fator genético desconhecido e que possa alterar os resultados). A randomização adequada deve ser feita com números aleatórios gerados por computador (também existem tabelas apropriadas) que são colocados em envelopes lacrados numerados que são abertos imediatamente antes da aplicação do tratamento. Métodos não adequados de randomização (quasi-randomizados) incluem, por exemplo, fazer cirurgia por laparoscopia 2as e 4as feiras e por laparotomia 3as e 5as feiras, ou então fazer uma cirurgia por laparoscopia e outra por laparotomia (alternando as vias). Estes métodos propiciam falhas na distribuição aleatória, mesmo que inconscientemente. Por exemplo, o cirurgião (ou quem encaminhou a paciente para a cirurgia e que conhece o esquema do estudo) pode achar a paciente muito obesa para a laparoscopia e subliminarmente (ou propositalmente?) adiar a cirurgia por um dia, coincidindo com a vez da laparotomia. A randomização adequada evita este tipo de erro na maioria das vezes. Entretanto, a randomização bem feita não garante a homogeneidade dos grupos (principalmente com amostras pequenas). É de bom tom verificar antes da análise dos dados se houve realmente uma distribuição semelhante dos pacientes (particularmente das características que influenciam diretamente no resultado, como: estádio da doença, idade, peso, etc..). Grupos não-balanceados podem enviesar os resultados.

Deve-se também estar atento se o método utilizado na mensuração do evento final de interesse foi o mascaramento duplo (duplo-cego). Isto implica que nem o paciente e nem o profissional que está fazendo a avaliação (p.ex. verificar o grau de dor no pós-operatório em pacientes que usaram ou não marcaína na ferida operatória) sabem qual tratamento foi aplicado. O médico pode, inconscientemente, não valorizar as queixas das pacientes que pertencem ao grupo do novo tratamento, falseando os resultados. O próprio paciente pode ser simpático a um determinado tipo de tratamento e não informar ao médico todas as queixas que tem. O método duplo-cego tenta eliminar este potencial tipo de erro. Nem sempre existe a possibilidade de se conduzir um estudo duplo-cego (comparação entre tratamento clínico versus cirúrgico), porém não se deve deixar de utilizá-lo quando possível.

Outro aspecto importante é o tempo de seguimento (follow-up). Em primeiro lugar é preciso certificar-se que o tempo de seguimento foi o suficiente para avaliar o evento final de interesse. Por exemplo, na transecção laparoscópica dos ligamentos útero-sacros, com o objetivo de aliviar a dismenorréia, o tempo de seguimento deve ser pelo menos superior a 1 ano, pois sabe-se do número elevado de recidivas após este período. Outro aspecto relevante é verificar se o percentual de pacientes que abandonaram o seguimento foi semelhante entre os diversos grupos. Taxa de seguimento inferior a 70% praticamente inviabiliza a análise dos dados, pois o abandono pode ter acontecido por efeitos colaterais ou até pelo óbito decorrente do tratamento.

Os erros mencionados anteriormente são sistemáticos, diferente dos erros aleatórios, que podem acontecer quando trabalhamos com qualquer amostra. A análise estatística adequada visa identificar se

as diferenças obtidas nos resultados foram por conta dos erros aleatórios ou se a diferença realmente existe entre os tratamentos aplicados. Os conceitos básicos da estatística serão abordados no próximo volume da revista.

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Original Article

Prevalence Study of Esophageal HPV Infection in Patients with Megaesophagus and Correlation with *in situ* and 24-Hour PH Measurement

Estudo da Prevalência do HPV em Esôfago de Portadores de Megaesôfago e a Correlação com o PH *in situ* e de 24 Horas

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ABSTRACT

Introduction: Studies have clearly demonstrated an association between infection with human papillomavirus (HPV) and malignant epithelial lesions. This relationship seems to be well established for squamous cell carcinoma of the uterine cervix, for which high- and medium-risk HPV types are associated with more than 95% of cases. A literature review correlating esophageal carcinoma with the presence of HPV demonstrated an association in 22.9% of cases when *in situ* hybridization was used and in 15.2% of cases when PCR was used for detection of the virus. The incidence of esophageal cancer has been shown to be 100 to 150 times higher among patients with megaesophagus compared to the general population. **Methods:** Fifty patients with megaesophagus ranging in age from 27 to 68 years (mean: 58.0) and 20 patients without esophageal pathology ranging in age from 52 to 70 years (mean: 59.9) were studied prospectively. In the study group, 29 patients were males and 21 were females. *Primers* specific for detection of HPV 16 and 18 used for the amplification of viral DNA by PCR. The measurement of *in situ* pH was performed using a SENTRON digital pH meter, with a scale of 1 to 14. 24-hour pH monitoring was conducted using the DIGITRAPPER MKIII, with the sensor probe positioned 5cm above the lower esophageal sphincter (LES). **Results:** HPV was detected in 19 (63.3%) of the 30 patients with megaesophagus studied, but in only three (16.7%) of the 18 controls, a difference that was statistically significant. HPV subtype 16 was detected in 15 cases. Positivity for HPV was significant in patients with megaesophagus and presented more percentage of time of pH in 24 hours between 5 and 6. **Conclusions:** These results demonstrate that the pH of the esophageal fluid ranges from 4 to 6 in patients with megaesophagus and shows a direct relationship with the presence of HPV. Subtype 16 was the most frequent HPV type.

Key words: 24 hour pH measurement; HPV; esophageal neoplasm.

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INTRODUCTION

Esophageal cancer is among the highest incident cancers in Brazil, with an estimated 10,630 new cases in 2010. This cancer is associated with heavy consumption of alcoholic beverages and tobacco products and other conditions such as nutritional deficiencies, achalasia, caustic lesions, and HPV infection.[1]

Many publications have irrefutably demonstrated an association between human papillomavirus (HPV) infection and malignant epithelial

lesions. For squamous cell carcinoma of the cervix this relationship appears to be well established,[2] and medium and high risk types of HPV are associated with more than 95% of the cases of cervical carcinoma globally.[3]

A review of the literature seeking to establish if there is a correlation between the presence of HPV and esophageal carcinoma, found an association in 22.9% of cases when *in situ* hybridization was used and in 15.2% of cases when PCR was used.[4]

There are currently 15 types of oncogenic HPV described as directly associated with genital and extra-genital neoplasias, with subtypes 16 and 18 predominating in 80% of cancers of the cervical canal[5] and 60 to 70% of cancers of the esophagus.[6]

In the literature there is geographic variation in this association; it is most characteristic of areas where squamous cell carcinoma of the esophagus is most prevalent, principally in South Africa, where the association was present in 46% of cases[7], and in China, where it occurred in 34.4%[8] to 65.5%[9] of cases.

In a study exploring the relationship between the presence of vaginal bacteria and HPV infection in pregnant women, a higher prevalence of vaginal pH exceeding 4.5 was noted in women infected with HPV, suggesting a relationship between an increase in vaginal pH and the presence of HPV.[10]

According to Pajecki *et al*., 2003, patients with Chagasic megaesophagus have a 33-fold greater risk of developing esophageal carcinoma, due to the production of N-nitrous compounds in the lumen of the organ that is mediated by bacteria in suspension in the stasis liquid causing chronic contact of these carcinogens with the esophageal mucosa.[11]

Several studies have found high rates of prevalence of HPV in squamous cell carcinomas of the esophagus.[12,13,14] It is known that the likelihood of developing this neoplasm is much greater in the presence of megaesophagus; however, the prevalence of HPV in this esophageal pathology has not been investigated. The objective of the present study is to evaluate the prevalence of **high risk** HPVs in the megaesophagus and their relationship with an increase in cases of neoplasm of the megaesophagus, and also correlate the esophageal pH with the presence of HPV.

METHODS

In a prospective study, 50 patients with megaesophagus followed by the Gastrointestinal Surgery Service of UFTM and 20 patients without esophageal pathology that constituted a control group were studied.

All patients underwent contrast radiography of the esophagus, stomach and duodenum (Upper GI series) and Upper Gastrointestinal Endoscopy (UGE).

The measurement of *in situ* pH was performed using a SENTRON digital pH meter, with a scale of 1 to 14.

24-hour pH monitoring was conducted using the DIGITRAPPER MKIII, with the sensor probe positioned 5cm above the lower esophageal sphincter (LES).

Biopsy fragments of the esophagus collected were immersed in 1.0 ml of TRIZOL® (Invitrogen™, Life Technologies, Carlsbad, California, USA), according the manufacturer's protocol and stored in a freezer at -70°C for later extraction of RNA. HPV was investigated using **Polymerase Chain Reaction** (PCR). Primers specific for HPV 16 and 18 were used to amplify the viral DNA. The amplified products were subjected to electrophoresis in a 10% polyacrylamide gel and stained with silver.

For the statistical analysis, a non-parametric analysis of variance (ANOVA) using Kruskal-Wallis and Mann-Whitney tests was performed. Results were considered statistically significant when $p < 0.05$.

RESULTS

The prospectively studied cohort included 50 patients with megaesophagus age 27 to 68 (mean age 58.0) and 20 patients without esophageal pathology age 52 to 70 (mean age 59.9). The study group included 29 men and 21 women; in the control group 10 subjects were women. Two patients had to be excluded from this group because they had alterations in their 24 hour pH monitoring. The most relevant clinical findings in the study group were concomitance of Chagasic megacolon in 19 and cholelithiasis in 15 patients, and the presence of cholelithiasis in 8 subjects in the control group. An analysis of the detection of HPV in both of the groups found no significant different with regard to gender, age, and the presence of cholelithiasis. The mean *in situ* esophageal pH was 6.5 in the study group (range 5.3 to 7.3) and 5.8 in the control group (range: 5.0 to 6.5). In relation to 24 hour pH monitoring, in all 50 cases of megaesophagus, it was noted that the percentage of the time the pH > 5 and < 7 (minimum 64% and maximum 99.5%) demonstrated a

acidification of the esophageal fluid, probably stemming from the fermentation of liquid residues in the setting of esophageal stasis with the formation of weak acids. In all of the 18 cases of the control group the pH > 6.3. In analyzing the 70 patients with regard to the pH range, the *in situ* pH value fell within the range measured during 24 hour pH monitoring in only 31 patients (44.3%). 24 pH monitoring is more sensitive and reliable for the analysis of the pH of esophageal liquid.

Of the 50 patients with megaesophagus, 30 patients were analyzed for the presence of HPV, and 19 (63.3%) were found to have HPV. Among the 18 controls analyzed, HPV was detected in three (16.7%). The presence of HPV was significantly greater in the group with megaesophagus than the control group. The presence of HPV was greater in grades III and IV than in grade II, a difference that was statistically significant (Figure 1).

Of the 22 cases where HPV was detected, 15 were HPV subtype 16. Subtype 18 was detected in 4 cases, including two of cases with subtype 16.

The correlation of a pH measurement < 4 and the detection of HPV in the megaesophagus was not statistically significant (Figure 2). However, the detection of HPV in the megaesophagus was significantly greater when the pH of esophageal fluid was in the range of 5 to 6 (Figures 3 and 4).

DISCUSSION

Infection by the Human Papillomavirus (HPV) is directly associated with cervical cancer, carcinoma of the esophagus, anal cancer and cancer of the penis. [15]

In a meta-analysis of 15 articles with 980 specimens, the presence of HPV was detected in 46.9% of cases. Subtypes 16 and 18 were the subtypes most commonly associated with carcinoma of the esophagus.[16]

In this study, the presence of HPV was significantly greater in patients with megaesophagus (63.3%) than in controls (16.7%). In the literature there are no articles which investigated the presence of HPV in patients with megaesophagus without neoplasia.

Birgisson *et al.*, 1997, studying the cause of achalasia analyzed myotomy muscular fragments (HELLER) in patients with idiopathic megaesophagus and did not detect the presence of HPV, Herpes virus, or measles.[17]

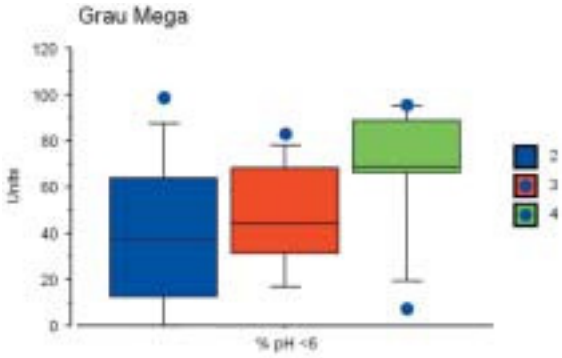

Figure 1 *– Relationship between the presence of HPV and the degree of megaesophagus (p=0.020).*

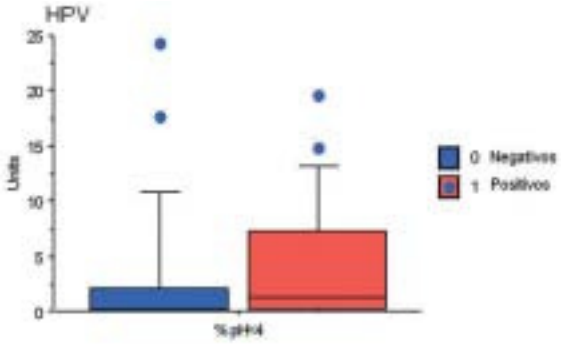

Figure 2 *– Relationship between the presence of HPV and period of time with pH<4 (p=0.14).*

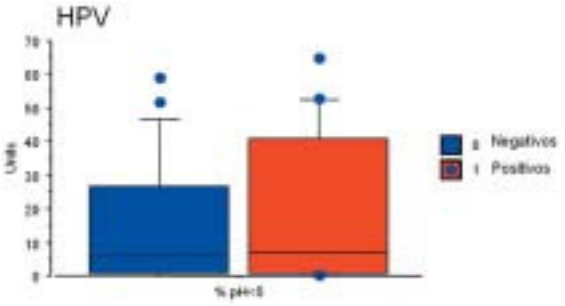

Figure 3 *– Relationship between the presence of HPV and the period of time with pH<5 (p=0.01).*

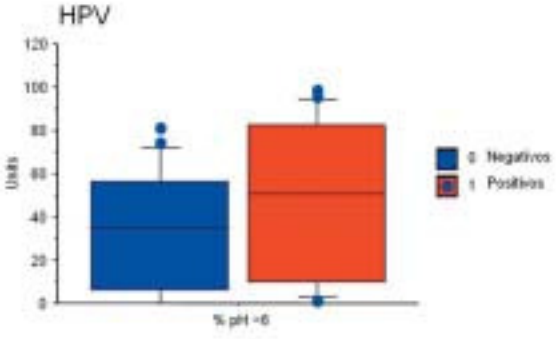

Figure 4 *– Relationship between the presence of HPV and the period of time with pH<6 (p=0.014).*

In this study, subtype 16 was the most commonly detected, and subtype 18, when found was associated with concomitant presence of subtype 16 present in two cases. These data corroborate the study of Zhao *et al*, 2009 that detected the presence of HPV in 88.1% of samples of esophageal carcinoma analyzed, with 19 specimens (45.2%) positive for HPV 16 and eight (19.9%) samples positive for HPV 18.[18]

Patients with megaesophagus have a rate of association of with esophageal cancer that varies from 100 to 150 times that encountered in the general population, probably from the chronic irritation of stasis liquid with weak acids from fermented food debris. Crema *et al*, 2002, detected an increased presence of bacteria in 91.4% of biopsy fragments of the esophagus in patients with megaesophagus.[19]

Da Silva *et al*, 2004, observed that the acidification of the vagina was associated with the presence of HPV.[10] Given that patients with megaesophagus have stasis, proliferation of bacteria with fermentation of food debris, production of weak acids, and consequently acidification of esophageal fluid, it was observed in this study that the *in situ* pH measurement was not as sensitive as 24 hour pH monitoring, which demonstrated acidification of the esophagus in all of the cases, with a pH in the range of 5 to 6 the most common. It was also noted that the presence of HPV can be correlated with a pH of esophageal fluid in the range of 5 to 6.

CONCLUSIONS

Based on these results, it can be inferred that esophageal liquid in patients with megaesophagus has a pH between 4 and 6. Detection of HPV is greater in patients with megaesophagus; the pH range with the highest rates of HPV detection was between 5 and 6. HPV Subtype 16 was the most frequently encountered.

RESUMO

Introdução: Diversas publicações têm demonstrado de maneira irrefutável a associação entre infecção pelo papilomavírus humano (HPV) e lesões epiteliais malignas. No carcinoma cervical uterino de células escamosas essa relação parece estar bem estabelecida, e os tipos de HPV de alto e médio risco estão associados a mais de 95% dos casos. Em estudo de revisão da literatura, procurou-se correlacionar o carcinoma esofágico e a presença do HPV, detectando uma associação de 15.2 a 22.9% na dependência da técnica utilizada. Nota-se que a incidência de neoplasia de esôfago associada ao megaesôfago é de 100 a 150 vezes maior que na população geral. **Metodologia:** Foram estudados prospectivamente 50 portadores de megaesôfago com idades variando de 27 a 68 anos (média de 58,03) e 20 pacientes sem esofagopatia com idades variando de 52 a 70 anos (média de 59,87 anos). No grupo de estudo, 29 pacientes eram do sexo masculino e 21 do feminino. Para amplificação do DNA viral pelo método de PCR utilizou-se *primers* específicos para detecção dos HPVs 16 e 18. A Medida do pH *in situ* foi realizada utilizando-se o pH meter digital SENTRON, com escala de 1 a 14. A pHmetria de 24h foi realizada com auxílio do DIGITRAPPER MKIII, sendo o sensor da sonda posicionado 5cm acima da região do esfíncter inferior do esôfago. **Resultados**: Dos 30 pacientes portadores de megaesôfago, detectou-se positividade para o HPV em 19 pacientes (63,34%) e dentre os 18 controles somente 3 (16,67%) foram positivos. Notou-se que em 15 casos, o subtipo prevalente foi o HPV16. A positividade do HPV foi significante nos portadores de megaesôfago e apresentaram maior percentual de tempo de pH nas 24 horas entre 5 e 6. **Conclusões:** Notou-se que o líquido esofágico nos portadores de megaesôfago apresentou pH entre 4 e 6 e com maior positividade do HPV, sendo o subtipo 16 o mais encontrado.

Palavras-chaves: pHmetria de 24 horas; HPV; neoplasia de esôfago.

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Brazilian Journal of Videoendoscopic Surgery

Original Article

Endoscopic Breast Surgery Applied To Benign Tumors

Cirurgia Endoscópica de Mama Aplicada a Tumores Benignos

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ABSTRACT

Introduction: Endoscopic Surgery applied to breast tumors, benign and malignant, has recently been analyzed, it seems to have the potential to become an alternative approach with good clinical and aesthetic results. In this report we present a case of breast fibroadenoma and discuss the application of the endoscopic surgery for breast tumor resection. **Methods:** A 22-year-old woman who had a 40 x 40 mm tumor in the lateral region of the right breast. It was diagnosed as a fibroadenoma tumor on the basis of ultrasound and fine-needle aspiration cytology. In the supine position under general anesthesia, a 12 mm skin incision was made below the mid-axillary line. The working space was made with blunt dissection and an insufflation with CO_2 gas pressure of 6 mmHg. Two 5 mm working ports were inserted along the anterior axillary fold two fingerbreadths cranial and caudal to the 12 mm port. Monopolar scissors performed the dissection around the tumor. After the tumor was isolated from all circumferences it was pulled out through the 12 mm port and taken out in two parts. **Results:** The operation time was 195 minutes and the postoperative course was uneventful. The patient was discharged on the second day postoperative. There was no postoperative collection or upper limb symptoms suggesting no injury to axillary structures. The cosmetic outcome was gratifying. **Conclusions:** The endoscopic surgery for benign breast tumors is a safe and technically feasible method to treat large benign tumors and provides cosmetic benefits.

Key Words: Endoscopic Breast Surgery, Breast Tumor, Cosmetic Outcome.

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INTRODUCTION

As a consequence of the proliferation of "minimally invasive" operating techniques endoscopic surgery has been widely used in different surgical specialties and has been applied to breast surgery since the mid-1990's.[1] In 1998, Kitamura and her colleagues[2] reported that with the endoscopic surgery of benign breast tumors they could obtain a more satisfying cosmetic outcome as compared to conventional surgery. More recently endoscopic surgery for malignant breast tumors has been considered; it seems to have the potential to become an alternative approach with good clinical and aesthetic results. [3-8]

Endoscopic breast surgery has not been widely adopted because it was not regarded as less invasive than the conventional surgery and because of several factors including: 1) a steep learning curve related to the challenges posed by the absence of a natural well-contained space, (as in the case of pleural and peritoneal cavities) that in the breast make it difficult to execute intracavitary surgical maneuvers; 2) the time required to carry out the procedure; 3) numerous strategies – without a standard – for the creation of the work space: the ball dissector (used in laparoscopic herniorrhaphy),[2,9] blunt dissection followed by continuous insufflation using carbon dioxide[10] and the video-assisted approach;[3-8] and 4) many breast surgeons were not familiar with the endoscopic procedures.

We describe a new method of endoscopic resection of benign breast lesions by creating a subcutaneous space maintained with continuous insufflation with carbon dioxide through the use of small axillary incisions that provides an anatomically contiguous area for creating access while preserving a scar-free breast. This case report is the first report of endoscopic surgery applied to breast lesions in Latin America.

MATERIALS AND METHODS

A 22-year-old woman was referred to the Surgery Service II of Caracas University Hospital, Central University of Venezuela for assessment of a palpable right breast lump. She had detected the breast lump three years earlier during self-examination and thought it was slowly growing. She complained of mastalgia, but denied nipple discharge, skin changes, or systemic symptoms. She had no personal or family history of breast cancer and had never used the oral contraceptive pill. Clinical examination revealed a tender, mobile 40 x 40 mm solid mass in the lateral region of the right breast. It was diagnosed as a fibroadenoma tumor on the basis of ultrasound and fine-needle aspiration cytology. We obtained her informed consent to perform the endoscopic excision of the tumor.

SURGICAL TECHNIQUE:

The surgeon and the first assistant are placed by the side of the breast to be dissected, with the monitor set above the patient's head. The endoscopic monitoring system is a product of the Olympus Optical Co. The endoscope is rigid and straight, 10 mm in diameter, at 0°. We use conventional laparoscopic tools with a monopolar coagulator.

Patient Positioning: In the supine position under general anesthesia, the upper limb on the operative side is raised and abducted to the patient's head frame, to avoid disturbing the operative maneuver, particularly toward the caudal direction. A roll is placed under the ipsilateral scapular region and the operating table is angled laterally 30°. (Figure 1)

Trocars Placement: A 12 mm skin incision is made below the mid-axillary line, at the nipple level. Through this incision a rigid endoscopic of 0º is introduced and fixed with a purse-string suture. Two 5 mm incisions are made two fingerbreadths cranially and caudally from the 12-mm incision. (Figure 2)

Creating the working space: The subcutaneous space is opened with blunt dissection with a 12 mm bladeless trocar in the avascular plane between the skin of the breast and the anterior surface of the mammary gland at the superior margin of the lesion. The advance toward the breast is guided by palpation of the trocar with the left hand of the surgeon. A CO_2 tube is connected to the port and in the dissected space a constant CO_2 flow is maintained by adjusting the rate of insufflation of the gas so as not to exceed 1.5 liters/minute, at a pressure between 6 and 8 mmHg that maintains the workspace. The 0° rigid scope is inserted and sweeping movements are made with it around the tumor, completing the creation of the working space, while taking care to avoid blood vessels passing through the subcutaneous tissue. 5 mm

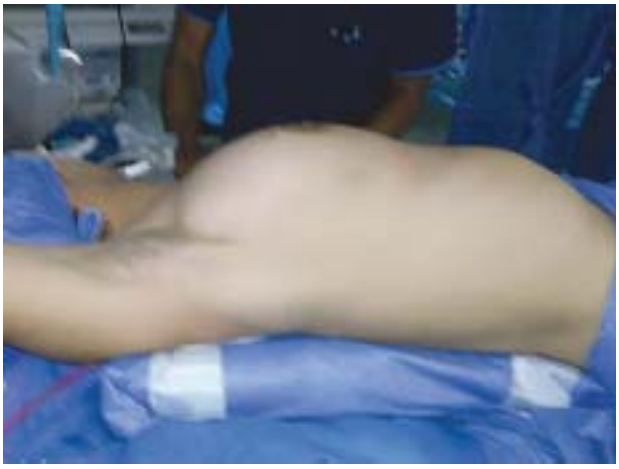

Figure 1 - *Patient Positioning.*

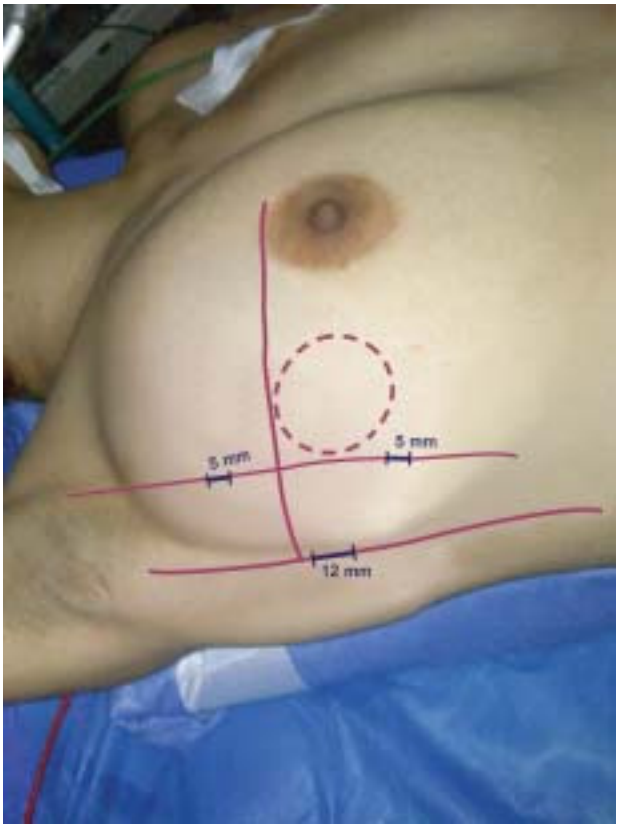

Figure 2 - *Trocar Placement.*

trocars are then introduced in a triangle under endoscopic control. (Figure 3)

Dissection Performed: The dissection is continued around the tumor by using the laparoscopic dissector and laparoscopic monopolar scissor. (Figure 4)

Exteriorization and extraction of the tumor: After the tumor was isolated from all circumferences it was pulled out with a grasper through the 12 mm port and taken out in two parts. A Penrose drain was inserted and left in the dissected cavity.

COSMETIC EVALUATION

The patient was examined four, seven and thirty weeks after surgery. We devised a scoring system for evaluating the cosmetic outcome with 5 items (ABNSW)[8]. The five items are: asymmetry (A), breast shape (B), nipple shape (N), skin condition (S) and wound scar (W). Each item is scored on a 0 to 3 scale: 0: poor, 1: fair, 2: good, 3: excellent. These 5 item scores are then totaled, with a maximum ABNSW score of 15. Results were defined as follows: 15: excellent; 11-14: good; 6-10: fair; 5 or less: poor.

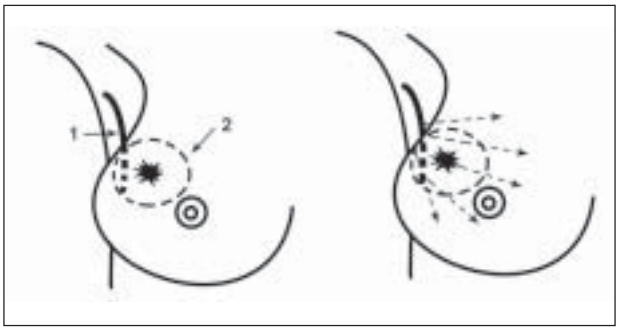

Figure 3 - *Creating the Working Space. 1. Midaxillary Incision. 2. Tumor.*

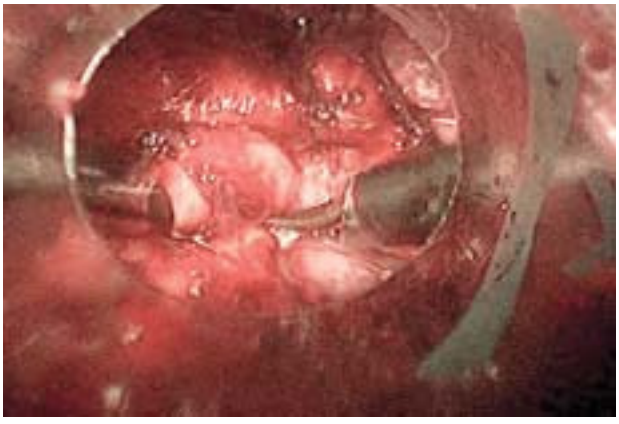

Figure 4 *- Dissection Performed. Endoscopic View.*

RESULTS

The operative time was 195 minutes. The postoperative course was uneventful. The patient was discharged on the second day postoperative. There was no postoperative fluid collection or upper limb symptoms suggestive of injury to axillary structures. The cosmetic outcomes were subjectively satisfying. The ABNSW score was 14, defined as very good. The pathological report was Fibroadenoma.

DISCUSSION

Benign breast masses can be followed periodically, but some factors – such as palpable mass, pain, growth and peace of mind – may lead patients to choose removal. Surgical resection has been the standard of care, with an incision made directly in the breast where the tumor is located or by circumareolar incision. Both often yield unsatisfactory aesthetic results, which is why several non-surgical options have been developed including vacuum-assisted biopsy,[11,12] radiofrequency ablation,[13,14] laser therapy,[15] and cryotherapy,[16,17] each with its own limitations.

Women have concerns about the cosmetic outcomes of benign breast tumor resections.[18] The use of endoscopic breast surgery, although still invasive, moves the surgical wound to a less conspicuous site, like the axilla.

Endoscopic surgery of the breast was reported in the early 1990s in plastic surgery[19] and has been employed since as a method for excision of benign and malignant breast tumors with good aesthetic and clinical outcomes. The endoscopic resection of benign tumors could be performed via the retromammary space and it was the most reported access.

We have described the blunt dissection technique – called the subcutaneous tunneling method – we use to create the workspace, separating the breast skin from the mammary gland tissue.[20] The transaxillary approach provides easy access. We work around the tumor in an avascular plane. This technique reduces surgical scarring, has excellent cosmetic results, and was well accepted by the patient. Although it is a time-consuming, the procedure can

be used in women with peripherally located tumors up to 4 centimeters or in women with multiple tumors where general anesthesia is justified. Further research must be done. Application of this technique in early stage breast cancer can also be considered and warrants further study.

RESUMO

Introdução: Cirurgia endoscópica aplicada aos tumores de mama, benignos e malignos, foi recentemente revisada e parece ter potencial para se tornar uma alternativa, com bons resultados clínicos e estéticos. Neste trabalho apresentamos um caso de fibroadenoma de mama e discutimos a aplicação da cirurgia endoscópica para ressecção de tumor de mama. **Métodos**: Mulher de 22 anos que apresntava um tumor de 40 x 40 mm na região lateral da mama direita. Foi diagnosticado como um fibroadenoma com base na ultrassonografia e na citologia aspirativa por agulha fina. Na posição supina, sob anestesia geral, uma incisão na pele foi feita 12 milímetros abaixo da linha axilar média. O espaço de trabalho foi criado com dissecção romba e por uma insuflação do CO2 com pressão de 6 mmHg. Dois portais de 5 milímetros foram inseridos ao longo da linha axilar anterior, dois dedos cranial e caudal ao portal de 12 mm. Tesoura monopolar foi usada na dissecção de todo o tumor. Depois que o tumor foi todo isolado, o mesmo foi puxado para fora através do portal de 12 mm e retirado em duas partes. **Resultados**: O tempo de operação foi de 195 minutos e o pós-operatório transcorreu sem intercorrências. A paciente recebeu alta no segundo dia pós-operatório. Não houve seroma ou sintomas do membro superior no pós-operatório, sugerindo que não houve danos às estruturas axilares. O resultado estético foi gratificante. **Conclusões**: A cirurgia endoscópica para tumores de mama é um método seguro e tecnicamente viável para tratar tumores benignos e proporciona benefícios cosméticos.

Palavras-chave: Cirurgia endoscópica da mama, tumor de mama, resultados estéticos.

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Brazilian Journal of Videoendoscopic Surgery

Original Article

Isoperistaltic Gastric Tube for Palliative Treatment of Esophageal Cancer - Postlethwait Technique: Proposal for a Videolaparoscopic Approach

Tubo Gástrico Isoperistáltico no Tratamento Paliativo do Câncer do Esôfago - Técnica de Postlethwait: Proposta de Abordagem por Videolaparoscopia

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ABSTRACT

Introduction: To demonstrate the laparoscopic technique for establishing a retrosternal bypass for the palliative treatment of advanced esophageal cancer by constructing a isoperistaltic gastric tube of greater curvature. **Methods**: The technique involves creating a bypass with a 3 cm wide gastric tube, with an average length of 30 cm and preservation of the right gastroepiploic vessels. The stomach is sectioned into "V", in a line parallel to the greater curvature with the aid of linear mechanical stapler, and a circular stapler in the antrum. The gastric tube made of the greater curvature is positioned retrosternally through the creation of an area below the xiphoid process to the sternal notch. The anastomosis of the proximal stump of the cervical esophagus with the proximal end of the gastric tube is performed a with a 25 mm intraluminal stapler. **Conclusion**: Isoperistaltic gastric tube by laparoscopy is feasible and reproducible and it is a good surgical method for the palliative treatment of advanced esophageal cancer.

Key words: Gastric tube, Postlethwait, Esophagus, Dysphagia.

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INTRODUCTION

Carcinoma of the esophagus is a very common disease in regions with low income populations and those accustomed to excessive ingestion of alcohol and tobacco abuse.[1,2] Over the past 40 years cure rates for esophageal carcinoma in Brazil have not improved significantly. With dysphagia the principal symptom, the diagnosis of esophageal cancer still occurs late when there is little chance of curative treatment.[1,3,4]

The palliative treatment of advanced or metastatic disease involves radiation therapy, use of prostheses and surgery. Radiation therapy offers a transitory improvement of the dysphagia in 50% to 70% of the patients who are able to complete the treatment (some 20% of cases are unable to complete radiation therapy).[4,5] Esophageal stenosis (26%), esophagotracheal fistulas (5%) and profuse hemorrhage (3%) are complications of radiation therapy, which worsens the clinical status of the patient.[6] Those who receive prostheses face restrictions in what foods they can eat and many have a sensation of a foreign body in the esophagus. Some 5% to 30% of cases have immediate complications such as perforations and bleeding; 7% to 34% experience late complications of migration or obstruction.[6,7] Mortality ranges from 0% to 29%.[6,8,9] The high cost of the prostheses/prosthetics means this treatment is not available in the majority of the public hospitals. Surgical procedures such as gastrostomy,[10] jejunostomy, and transpositions with the colon, jejunum or stomach[6] have been used for years for palliation, but are not free of complications. Among these, the isoperistaltic gastric tube has become one therapeutic option for treating the dysphagia and the esophagotracheal fistulas,[14] restoring the patient's pleasure in being able to feed himself by mouth.

The first reference to the isoperistaltic gastric tube perfused by the right gastroepiploic artery was by Dengel in 1930, who attributed the concept to Rutkowiski.[11] Only in 1979, did Postlethwait report the use of the isoperistaltic gastric tube to bypass an esophagus with advanced neoplasia.[12] Now with advances in the use of videosurgery in the treatment of cancer patients, we propose a videolaparoscopic approach for the surgery recommended by Postlethwait.

OBJECTIVE

To demonstrate a bypass procedure in a patient with advanced esophageal cancer, in which an isoperistaltic gastric tube of the greater curvature is positioned retrosternally with a cervical anastomosis as proposed by Postlethwait in 1979. The authors propose a videolaparoscopic approach for this technique.

TECHNIQUE

The technique involves the creation of a gastric tube close to 3 cm in width and with an average length of 30 cm and preservation of the right gastroepiploic vessels, which are responsible for its nutrition. The patient is placed in a lithotomy position, with a low pressure pneumoperitoneum, with the peritoneum in low pressure (10 mmHg) in order to prevent subcutaneous emphysema. The procedure begins with the passage/placement of five trocars (Figure 1). The first trocar (11 mm) is positioned in the umbilical scar for use of the optic and the occasional laparoscopic stapler. The second epigastric 5 mm trocar is for the vacuum and the spreader. Three more 12 mm trocars are placed in the right and left subcostal margins and left flank (which later will be withdrawn to permit the introduction of the 21 mm intraluminal stapler).

After positioning the surgeon between the legs of the patient and the first assistant on the left side (with the optic and the vacuum), one begins by sectioning the gastrocolic ligament so that the greater gastric curvature is isolated, preserving the arch of the right gastroepiploic artery in the direction of the short vessels to the angle of Hiss, completely freeing the spleen. This stage of the surgery is completed with the identification of the gastroduodenal artery close to the head of the pancreas and freeing possible adhesions of the pancreas to the stomach, which can hamper the mobilization of the tube toward the cervical region.

The stomach is then divided in a line parallel to the greater curvature with the aid of a linear mechanical stapler. This division extends from the antrum to the gastric fundus. Initially we transfix the stomach (entire wall – anterior and posterior) to the antrum 5 cm from the pylorus using a 21 mm intraluminal stapler (which, with an expansion of the incision, is introduced in the position of the 12 mm trocar in the flank,). After stapling the stomach and removing the stapler, a "ring" is formed that is approximately 1.5 cm in diameter, surrounded with staples (Figure 2). Next, we fashion a tube using the greater curvature, introducing a blue cartridge linear laparoscopic stapler in the "ring" previously created in the antrum toward the gastric fundus. The sectioned stomach resembles a "V", in which the part corresponding to the lesser curvature drains the distal esophagus in relation to the tumor, and the greater curvature will correspond to the tube. The blood supply for the tube which measures 3 cm in diameter and has an average length of 30 cm, is supplied by the right gastroepiploic artery, (Figure 2).

Finally, a left neck incision, eight to ten centimeters long, is made along the inner border of the sternocleidomastoid muscle from the middle third of the neck to the sternal notch. The platysma and pre-thyroid muscles are sectioned, the thyroid gland is moved medially, and the left sternocleidomastoid muscle is displaced. After dissection and sectioning of the cervical esophagus, the distal end is amputated by manual suturing in a single plane. A purse is fashioned for the positioning of the "head" of a 25 mm intraluminal stapler in the "stump" of the proximal esophagus.

The gastric tube of greater curvature is passed through a retrosternal path by creating a space with the sectioning of the round and falciform ligament, followed with a 5 cm opening of the peritoneum and aponeurosis just below the xiphoid process. The identification of this boney structure is critical for the creation of this space. After dissection of the xiphoid, the dissection is maintained with a 10 mm LigaSure™, preserving the plane of the sternum, until the surgeon's finger is identified in the sternal notch through the cervicotomy (Figure 3).

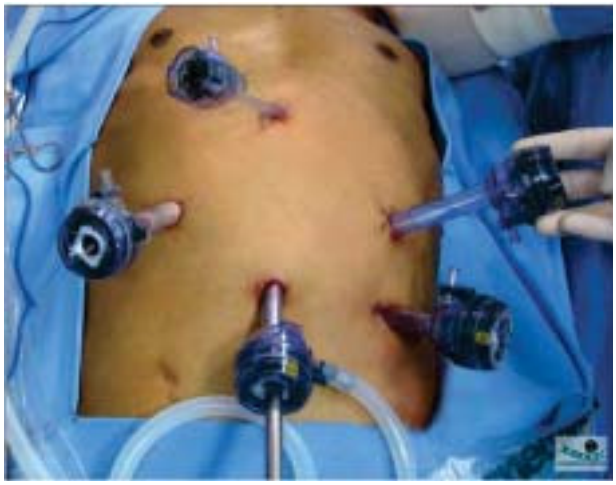

Figure 1 - *Trocar positions: 5mm epigastric, 11 mm umbilical, 12 mm at the right and left costal margins and the left flank.*

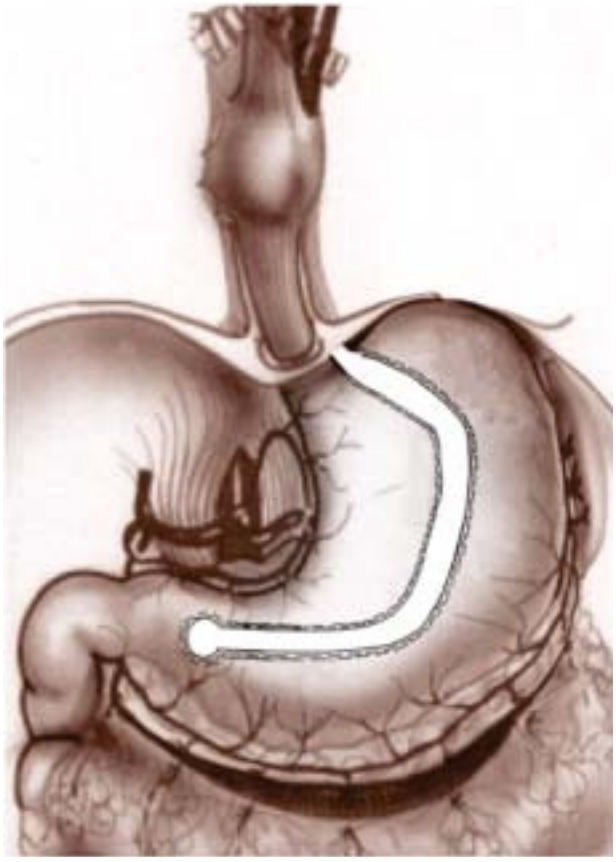

Figure 2[14] *- "Ring" in the antrum region with the stomach sectioned in the form of a "V", with the tube formed by the greater curvature with gastroepiploic vessels.*

Cardiac tape or a Levine gastric tube is passed to attach to the tip of the tube, so that it can be pulled to the cervical region under direct vision with the optic. This helps to ensure that the tube is not

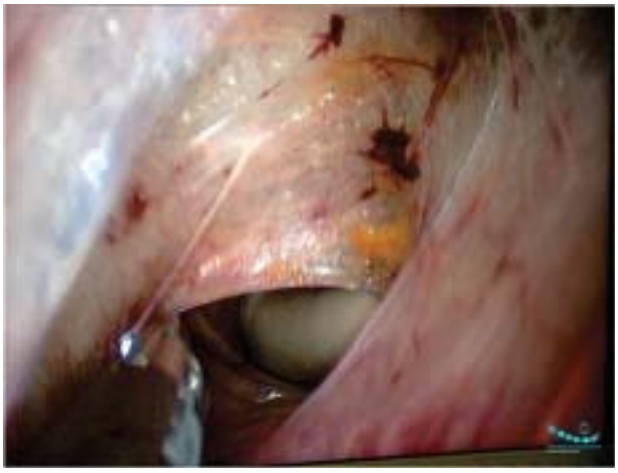

Figure 3 - *Dissection of the retrosternal space, with visualization of the finger of the surgeon in the sternal notch.*

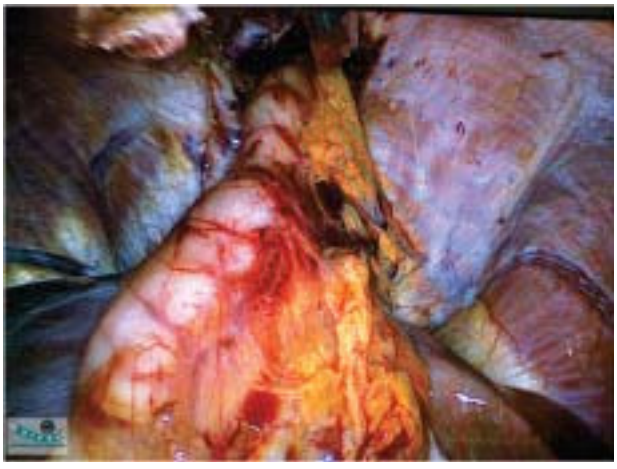

Figure 4 - *Final appearance of the retrosternal gastric tube.*

twisted and its anatomic position is maintained, and that the vascular arch is not subjected to excessive traction (Figure 4). One then proceeds with the anastomosis of the proximal stump of the cervical esophagus to the proximal end of the terminal-lateral gastric tube using a 25 mm intraluminal stapler. The excess tubing is sectioned using a blue load linear stapler. This procedure is completed with the positioning of a nasogatric feeding tube, which is removed postoperatively once the patient is able to swallow. We do not use drains in the thorax, nor in the abdomen.

DISCUSSION

The videolaparoscopic reconstruction of esophageal bypass using an isoperistaltic gastric tube constitutes a therapeutic option for patients in clinical

stages III and IV. These palliative surgeries seek to bypass the path that food normally transits in the esophagus, improving patients' quality of life. Given the difficulties many experience with stomas[13] just being able to feed oneself orally confers a psychological benefit. Performing the procedure laparoscopically seeks to diminish the morbidity, shorten the duration of hospitalization, and accelerate the recuperation of the patient.

CONCLUSION

We have shown that Postlethwait's surgery for the palliative treatment of advanced esophageal cancer, published in 1979,[12] can be completely reproduced using videosurgery. To date there is no such description cited in the Brazilian or international literature. We propose a new approach: the Postlethwait technique by videosurgery.

RESUMO

Objetivo: Demonstrar a técnica para confecção de um bypass com tubo gástrico isoperistáltico por via retroesternal, com a grande curvatura gástrica, para o tratamento paliativo do câncer de esôfago avançado por laparoscopia. **Métodos**: A técnica envolve a criação de um tubo de 3 cm de largura com preservação dos vasos gastroepiplóicos direitos. O estômago é seccionado em "V", em uma linha paralela à grande curvatura, com o auxílio de sutura mecânica linear e circular no antro. O tubo gástrico da grande curvatura é posicionado por via retroesternal, através da criação de uma área abaixo do processo xifóide até a fúrcula esternal. A anastomose do coto proximal do esôfago cervical com a extremidade proximal do tubo gástrico é realizado com grampeador intraluminal de 25mm. **Conclusão**: O tubo gástrico isoperistáltico por via laparoscópica é factível e reproduzível sendo um bom método para o tratamento cirúrgico paliativo do câncer de esôfago avançado.

Palavras-chave: Tubo gástrico, Postlethwait, Esôfago, Disfagia.

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Original Article

Laparoscopic Splenectomy in the Treatment of Childhood Hematologic Disorders

Esplenectomia Laparoscópica no Tratamento de Doenças Hematológicas da Infância

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ABSTRACT

Introduction: Spherocytosis, idiopathic thrombocytopenic purpura, and sickle cell disease are the most common indications for performing splenectomy in children. The aim of this study is to present our experience with laparoscopic splenectomy. **Material and methods:** A retrospective study was carried out analyzing the medical records of 86 patients. The following data were selected for analysis: age, sex, indications for splenectomy, presence of associated gallstones, presence of accessory spleens, surgical time, complications and hospital stay. **Results:** Age ranged from 6 months to 18 years with a mean age of 6.2. The weight ranged from 8 to 60 kg with a mean 23 kg. Splenectomy was performed by the following indications: sickle cell disease (45 cases), idiopathic thrombocytopenic purpura (23), Spherocytosis (11), thalassemia (3) autoimmune hemolytic anemia (1), myelodysplasia (1), Hodgkin's disease (1) and myelomonocytic leukemia (1). Cholelithiasis was diagnosed in six patients. Accessory spleens were found in 10 patients (12%). Bleeding was the more frequent intraoperative complication and in 5 patients (6%) caused the conversion to open surgery. Operative time ranged from 70 to 320 minutes with a mean of 160. Among early postoperative complications, one patient had pneumothorax and 3 had intra-abdominal fluid collection which resolved. Late complications included one patient with an umbilical incisional hernia and one patient with portal vein thrombosis. Hospital length-of-stay ranged from 2 to 21 days with an average of 3.2 and a median of 2 days. **Conclusion:** Laparoscopic splenectomy is a safe and effective alternative to open splenectomy.

Key words: Laparoscopy, splenectomy, portal vein thrombosis, children. Sickle cell.

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INTRODUCTION

Hematological disorders constitute the main indication for splenectomy in childhood. Spherocytosis, idiopathic thrombocytopenic purpura (ITP) and sickle cell anemia (SCA) make up the majority of cases. Splenectomy was performed exclusively via an open approach until 1991, when DELAITRE and MAIGNIEN performed the first laparoscopic splenectomy in an adult patient.[1] TULMAN and colleagues in 1993 performed the first laparoscopic splenectomy in children.[2] Since then, this technique has been gaining popularity due to accumulated experience and technological advances. The aim of this study is to present a single service's experience with laparoscopic splenectomy in children.

METHODS

We conducted a retrospective study, analyzing the medical records of 86 children and adolescents who underwent elective laparoscopic splenectomy performed in Pediatric Surgery Service of the Darcy Vargas Children's Hospital in the period from July 2002 to March 2011.

The preoperative diagnosis and indications for splenectomy were established by the department of hematology and oncology, where patients were prepared for surgery and followed postoperatively.

Patients with a hemoglobin below 10 g/dl received packed red blood cells until the hemoglobin was between 10 and 12 g/dl. All patients received pneumococcal and meningococcal vaccines. The evaluation of patients with hemoglobinopathies included ultrasonography to assess the presence of associated cholelithiasis.

The laparoscopic technique involves inserting a 10 mm trocar in the umbilicus by the open technique. After creating the pneumoperitoneum, a 10 mm trocar is introduced in the left iliac fossa and two 5 mm trocars are placed, one subxiphoid and the other in the left anterior axillary line, below the rib cage. When cholecystectomy is also performed one more 5-mm trocar is employed in the right flank. The procedure begins with the opening of the gastrocolic ligament and extends along the entire gastric curvature and involves the short vessels. This maneuver exposes the pancreatic tail and splenic artery, which is ligated. Next the splenorenal and splenocolic ligaments are sectioned. Finally, the hilar vessels are sectioned after ligation with clips. Once completely freed, the spleen is placed into a plastic bag, crumbled into fragments, then eased out of the abdomen through a narrow incision.

The following variables were selected for analysis: age, sex, indication for splenectomy, presence of associated gallstones, presence of accessory spleens, surgical time, complications, and length of hospitalization.

RESULTS

Eighty six patients — 36 females and 50 males — underwent laparoscopic splenectomy. Age ranged from 6 months to 18 years with a mean of 6.2 and a median of 5.5 years. Weight ranged from 8 to 60 kg with a mean of 23 kg and median of 21 kg. Splenectomy was performed for the following indications: sickle cell anemia (45), idiopathic thrombocytopenic purpura (23), spherocytosis (11), thalassemia (3), autoimmune hemolytic anemia (1), myelodysplasia (1), Hodgkin's disease (1) and myelomonocytic leukemia (1). Cholelithiasis was diagnosed in six patients, who underwent concomitant cholecystectomy.

Accessory spleens were found in 10 patients (11%) and removed during the procedure. Bleeding was the most frequent intraoperative complication, and in 5 patients (6%) prompted conversion to open surgery. Another case was complicated by opening of the diaphragm. The operative time ranged from 70 to 320 minutes with a mean of 160 and a median of 150 minutes.

Among the early postoperative complications, one patient had a pneumothorax that required chest tube drainage and three patients had intra-abdominal fluid collections that were treated conservatively.

The late postoperative complications included one patient who was noted to have an incisional umbilical hernia, one patient who developed portal vein thrombosis, and one patient with ITP who initially evolved with a partial response to the splenectomy, and was found on ultrasound to have an accessory spleen that had not been diagnosed intraoperatively. Later this patient was found to have a platelet count of around 160,000/uL; free of symptoms the patient was not re-operated. Inpatient length-of-stay ranged from 2 to 21 days, with a mean of 3.2 and a median of 2 days. Follow-up ranged from one month to 8 years and 9 months.

DISCUSSION

For nearly a century splenectomy has been used in the treatment of hematologic disorders. Classically performed by open surgery, starting in 1991 they began to be performed laparoscopically, initially in adults[1] and since 1993 in children.[2]

Laparoscopic splenectomy is a procedure of high complexity, whose technical difficulty is directly related to the presence of adhesions to other organs and the relative size of the spleen.

Adhesions occur involving the abdominal wall, omentum, stomach, colon and retroperitoneum, and are more frequent in sickle cell anemia with various crises and splenic sequestration and in cases of splenic abscess. When present, their lysis constitutes the first step of the surgery; despite the additional difficulty they do not constitute a contraindication to the procedure.

Splenomegaly is more common in spherocytosis and in lymphomas. The definition of the degree of splenomegaly in a quantitative manner through measurements is very inexact because of the wide age range in which the procedure is performed. Murawski and cols consider very marked splenomegaly, one in which the spleen reaches the height of the iliac crest.[3] Splenomegaly until recently was considered a contraindication to the performance

of laparoscopy. Today this rule only applies to very pronounced splenomegaly that does not allow the mobilization of the organ and the visualization and exploration of the abdominal cavity in a safe manner.[3] Less marked splenomegaly may be addressed by laparoscopy; a maneuver that usually improves the technical conditions is the prior ligation of the splenic artery, which results in "autotransfusion" and a decrease in the size of the spleen. In ITP, on the contrary, the spleen usually is normal in size. However, in the presence of corticosteroid treatment, there may be visceral fat accumulation which complicates the dissection of the splenic hilum.

In our series the main indication for splenectomy was for SCD with splenic sequestration crises, unlike the literature in which spherocytosis and ITP are the leading indications.[4-6]

The main intraoperative complication was bleeding, which in five cases led to conversion to open surgery.

Of the five patients, three had sickle cell disease and two had spherocytosis. All presented with splenomegaly; those with SCD also had extensive adhesions. The rate of conversion to open surgery was 6% (n = 5), which compares with a range of 2 to 18% in the global literature.[4-10]

The identification and removal of accessory spleens is another important issue, since missing them may allow the condition for which the splenectomy may persist or there may later be a recurrence of symptoms. The incidence of accessory spleens was 12% in our sample, whereas in other series this rate varies from 4 to 28%.[6,7,10-14] The vast majority are located in the region of the tail of the pancreas, omentum and splenic hilum. The laparoscopic approach seems to imply an increased difficulty in locating them and they should be removed as soon as they are identified.

Surgical time is related to the learning curve, material available, anatomical conditions such as the size of the spleen and the presence or absence of adhesions. In our series the average was 160 minutes. On the other hand, the median duration of the postoperative hospital stay was 48 hours.

A review of the literature reveals that these two variables – surgical time and duration of the hospitalization – represent the most conflicting results when analyzing the open approach versus the laparoscopic technique. However, these authors[6,8,10,11] are unanimous in asserting that the longer duration of laparoscopic surgery is offset by a lower postoperative morbidity, a shorter hospital stay, a quicker return to normal activities, an earlier return to other treatments were postponed, as well as better aesthetic results.

The main postoperative complication occurred in one patient with spherocytosis who developed portal vein thrombosis (PVT), which was diagnosed about one year after the surgery when the patient experienced upper gastrointestinal hemorrhage due to bleeding esophageal varices. The estimated incidence of symptomatic PVT is between 0.07% and 2%, but the incidence found on routinely performed imaging studies can be between 7% and 10%. It is more frequent in adults. It is characterized by vague symptoms such as fever, vomiting, abdominal pain. DVT occurs in adults on average on the sixth day after splenectomy, but the period of time can vary up to 18 months. The occurrence of these symptoms after surgery involves the performance of Doppler ultrasound of the portal venous system. DVT occurs most frequently in patients suffering from myeloproliferative disorders, hemolytic anemia with splenomegaly and thrombocytosis large. Thrombosis occurs as frequently in open splenectomies as with laparoscopic splenectomies.[15-18]

CONCLUSION

Laparoscopic splenectomy is a safe and effective alternative to open surgery in the treatment of hematologic malignancies of childhood.

RESUMO

Introdução: Esferocitose, purpura trombocitopênica idiopática e anemia falciforme são as indicações mais comuns para a realização de esplenectomia em crianças. O objetivo desse estudo é apresentar a experiência com o uso da esplenectomia laparoscópica. **Métodos**: Foi realizado um estudo retrospectivo analisando os prontuários de 86 pacientes. Os seguintes dados foram coletados para análise: idade, sexo, indicação da esplenectomia, presença de colelitíase associada, presença de baços acessórios, duração da cirurgia, complicações e permanência hospitalar. **Resultados**: A idade variou de 6 meses a 18 anos com uma média de 6,2. O peso variou de 8 a 60 kg com uma média de 23 kg. A esplenectomia foi realizada pelas seguintes indicações: anemia falciforme (45); purpura trombocitopênica idiopática (23); esferocitose (11); talassemia (3); anemia hemolítica auto-imune (1); mielodisplasia (1), Doença de Hodgkin (1) e leucemia mielomonocítica (1). Colelitíase foi diagnosticada em 6 pacientes. Baços acessórios foram encontrados em 10 pacientes. O sangramento foi a complicação intra-operatória mais freqüente, sendo que em 5 pacientes (6%) determinou a conversão para cirurgia aberta. O tempo operatório variou de 70 a 320 minutos com média de 160. Entre as complicações pós-operatórias precoces, um paciente apresentou pneumotórax e 3 pacientes apresentaram coleção intra-abdominal. Entre as complicações pós-operatórias tardias, foi registrado um paciente com hérnia umbilical incisional e um paciente com trombose de veia porta. O tempo de internação variou de 2 a 21 dias com media de 3,2 e mediana de 2 dias. **Conclusão:** A esplenectomia laparoscópica é uma alternativa segura e eficaz no tratamento das doenças hematológicas da infância.

Descritores: Laparoscopia, esplenectomia, trombose veia porta, anemia falciforme, criança.

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ABREVIATIONS

ITP - Idiopathic Thrombocytopenic Purpura
FA - Falciform Anemia
PVT - Portal Vein Thrombosis

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Brazilian Journal of Videoendoscopic Surgery

Review Article

Hysteroscopic Permanent Female Sterilization

Esterilização Permanente Feminina por Histeroscopia

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ABSTRACT

Birth control is a necessity in society. Contraceptive methods facilitate family planning. The oral contraceptive pill (OCP) is the most popular temporary method. Female sterilization is a definitive method of contraception. The surgical approaches for female sterilization include laparotomy and minimally invasive techniques such as laparoscopy for tubal ligation (TL), and tubal occlusion by microdevices (ESSURE and ADIANA), guided by hysteroscopy, whose main advantages are: outpatient placement, no incisions and no anesthesia. ESSURE is composed of stainless steel, nitinol and Dacron. Its mechanism of action is attributed to the production of localized fibrous reaction. It is indicated for women who are secure in certain that they want definitive sterilization. It is especially beneficial to those with comorbidities that place them at increased surgical risk. It is contraindicated in pelvic inflammatory disease, steroid use and abnormal uterine bleeding. Other contraceptive methods should be used during the first three months after insertion of the microdevice, at which time an imaging test, such as hysterosalpingogram, plain radiograph (X-ray) or ultrasound should confirm tubal occlusion. The method achieves 99.8% efficacy. The most common complications are utero-tubal perforation and expulsion of the microdevice. Costs are similar to those of tubal ligation by laparoscopy and the learning curve is small.

Key words: tubal sterilization, Hysteroscopy, Intratubal microdevice, permanent contraception.

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INTRODUCTION

In modern society control of reproduction has become a necessity. Social and demographic issues compel man to seek methods that permit him to plan births. Family planning arose to respond to these issues. In Brazil family planning is regulated by Law No. 9263 enacted January 12, 1996.[1]

Contraception can be achieved by hormonal and non-hormonal methods, and by surgical sterilization. Among the non-hormonal methods the male preservative (condom) is the most used. Hormonal contraception is done with medications that contain sexual steroids (estrogen and progesterone) in the most varied formulations and routes of administration (oral, transdermal, vaginal, etc.), with the oral contraceptive pill (OCP) the most utilized.

In the second half of the last century, an American biologist Gregory Goodwin Pincus, working with an American gynecologist, John Rock, synthesized a compound, composed of estrogen and progesterone, which they called a "contraceptive pill". The Food and Drug Administration (FDA) approved this medication for clinical use in May 1960. Currently, around 80 million women around the world, and 9 million in Brazil, regularly use this medication. The oral contraceptive pill (OCP) was and continues to be, the most popular temporary contraceptive method worldwide.

With regard to efficacy, surgical contraception has a low incidence of failure, similar to the best contraceptive methods (Table 1).

The surgical approach for female sterilization can be by laparotomy (associated or not with a Caesarian section), mini-laparotomy, laparoscopy, mini-laparoscopy, vaginal (by anterior or posterior colpotomy) and, now, by a transcervical route guided by hysteroscopy (HSC).

Table 1 - Percentage of women in whom there was contraceptive failure during the first year of use and the Percentage that continued to use it at the end of the first year.

	Women who Accidently became Pregnant during the First Year of Use (%)		Women Who Continued to Use It at 1 Year (%)
Method	**Typical use**	**Perfect Use**	
No Method	85	85	
Spermicides	29	18	42
Abstinence	25		67
Rhythm method		9	
Ovulation method		3	
Symptothermal/Basal BodyTemperature		2	
Post-ovulation		1	
Coitus interrupted/Withdrawal	27	4	43
Cervical cap			
Women with children	32	26	46
Nulliparous women	16	9	57
Sponge			
Women with children	32	20	46
Nulliparous women	16	9	57
Diaphragm	16	6	57
Preservative (Condom)			
Female (Reality)	21	5	49
Male	15	2	53
Combined Pill and the Progesterone-only pill	8	0.3	68
Adhesive (Evra™)	8	0.3	68
NuvaRing	8	0.3	68
Intrauterine devices			
ParaGard[tm] (Copper T380A)	0.8	0.6	78
Myrena (Levonorgestrel T)	0.1	0.1	81
DepoProvera	3	0.3	70
Lunelle	3	0.05	56
Norplant[a] and Norplant II	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Source: Berek and Novak, 2008 (17).

The transvaginal route is considered minimally invasive surgery, is inexpensive, but would have a prolonged learning curve in Brazil where it is not performed frequently.

The approach most used in Brazil for tubal ligation is laparotomy, generally following Caesarian section. Since the 1950s laparoscopy has been gaining popularity as the approach for tubal ligation (TL), due to the fact that it can be used outside the context of pregnancy, and is associated with less pain, less blood loss, a shorter hospitalization, and a lower risk of infection, as well as a faster recuperation. Laparoscopy is an effective and safe technique; nevertheless the women is submitting herself to the risks of anesthesia and surgery, as well as the complications inherent in the procedure.

In the United States, the Center for Disease Control and Prevention (CDC) conducted the largest study of tubal sterilization, the Collaborative Review of Sterilization (CREST) study.[2] Jamieson and cols.

Table 2 - *Cumulative pregnancy rate in 1000 sterilization procedures performed from 1978 to 1987.*

Unipolar coagulation	7.5
Postpartum partial salpingectomy	7.5
Silastic ring (Falope or Yoon)	17.7
Interval partial salpingectomy	20.1
Bipolar coagulation (one point)	24.8
Bipolar coagulation (three points)	3.2
Hulka-Clemens Clip	36.5

analyzed 10,685 laparotomic and laparoscopic sterilizations (Table 2) performed between 1978 and 1987, with a 10 year follow-up. The accumulated failure rate of ligatures in this period was 1.85%. Among a total of 9,475 laparoscopic sterilizations, the complication rate varied between 1.17% and 1.95%. The probability was greater in patients with comorbidities (diabetes, obesity and previous surgeries) aggravated by the complications inherent with anesthesia.

Laparoscopy requires a surgical setting and general anesthesia; the efficacy approaches 99.5%, but there are intra- and post-operative complications, including 11 deaths/100,000 procedures.[3] Although minilaparoscopy using a 5 mm optic can be performed on an outpatient basis with local anesthesia and conscious sedation, both are techniques that invade the abdominal cavity.

Other techniques, such as Natural Orifice Transluminal Endoscopic Surgery (NOTES), seek access to the Fallopian tubes though natural orifices such as the vagina (anterior or posterior colpotomy). There are currently few statistics in the literature.

Hysteroscopy (HSC) is a slightly invasive method that uses the cervical canal to access the uterine cavity and the tubal ostia. The technique of hysteroscopy established itself with the work of Jacques Hamou.(3) Since 1980, there have been significant improvements in the image quality, as well as the creation of an operative canal in diagnostic hysteroscopy, that with its narrow caliber, making it possible to perform major procedures on an outpatient basis.

In the 1990s two permanent female contraception systems were developed, the ESSURE and ADIANA systems [4], that permit outpatient tubal occlusion through a transcervical route, without incisions or the need for anesthesia.

In 2002 the Food and Drug Administration (FDA) approved the first transcervical sterilization method, the ESSURE Permanente Birth Control System (Conceptus Inc., San Carlos, CA). ESSURE is a microdevice consisting of an internal spiral made of stainless steel, covered by Dacron fibers and an external dynamic spiral composed of a nickel-titanium alloy called nitinol. It is 4 cm in length and 0.8 mm in diameter, reaching 1 to 2 mm when expanded.

In 2009 the FDA approved a second transcervical sterilization method, the ADIANA Permanent Contraception System (Hologic Inc., Bedford, MA). The ADIANA sterilization method (Figure 1) combines radiofrequency-controlled cauterization, for a period of one minute, which causes a 5 mm lesion in the tubal mucosa, followed

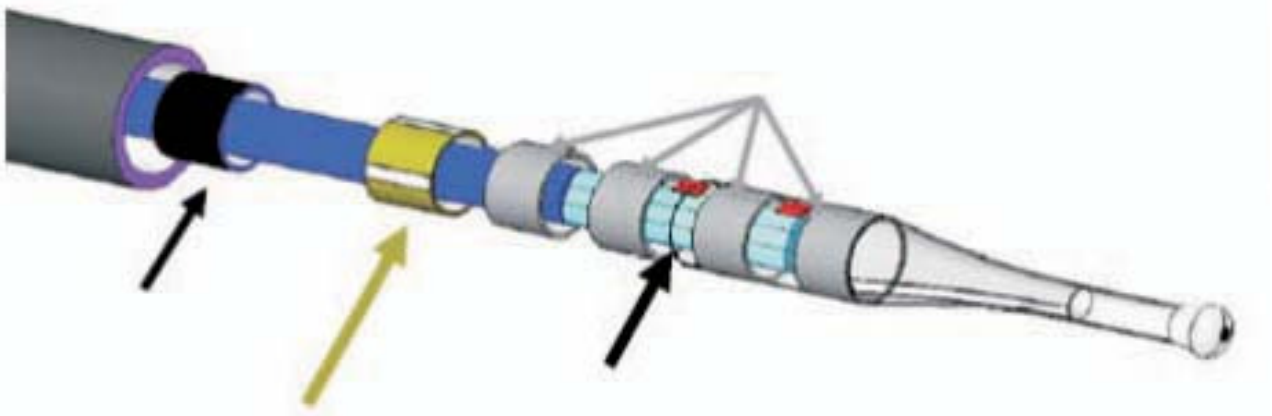

Figure 1 - *Adiana Permanent Contraception System*
Source: Reviews in Obstetrics Gynecology, 2009.

immediately by the introduction of a 3.5 mm silicone matrix that is implanted in the interior of the Fallopian tube, using a catheter inserted in the tubal ostium via hysteroscopy. Occlusion is achieved by the growth of fibroblasts around the matrix, which serves as a permanent substrate for occlusion of the tubal lumen. The occluded tube should be evaluated three months after the placement of the device by hysterosalpingogram (HSG). Such imaging actually only demonstrates where the contrast "stops", as the ADIANA itself cannot be visualized with X-rays. It can, however, be visualized with ultrasound.

The one-year and two-year accumulated failure rate for the ADIANA system is 1.08% and 1.82% respectively. In the CREST study, the failure of ADIANA was higher than all the permanent methods evaluated in the study except for the use of spring clips.[5]

Recently, the National Agency for Sanitary Surveillance (ANVISA) authorized use of the ESSURE system in Brazil. The national health care system – *Sistema Única de Saúde* (SUS) – is carrying out viability studies of intratubal microdevices for permanent sterilization. In Santa Catarina, the state legislature (Assembléia Legislativa) passed and the governor signed Law 14,870 that in its first article states: surgical procedures called tubal ligation, vasectomy, and transcervical sterilization performed in the public hospital network that are covered by SUS are free to the citizens who are residents of state of Santa Catarina.

Various publications have reported success rates for the outpatient placement of ESSURE ranging from 85% to 99.8%.[5] In the context of advances in permanent female contraception, the objective of this article is to review the literature about ESSURE. At the present time ADIANA is not available in the Brazilian market.

ESSURE'S COMPOSITION AND MECHANISM OF ACTION

The ESSURE system consists of a handle, a catheter driver, the microdevice and a "dry flow" introducer (Figure 2). The handle has a rotating control dial and a trigger button (Figure 3). The catheter houses the microdevice, which has a non-traumatic spherical tip (Figure 4). The dry-flow introducer has an anti-reflux valve which maintains the intrauterine pressure and protects the distal part of the device.

The mechanism of action is through stimulation of tissue proliferation of fibroblasts, macrophages, foreign body giant cells and plasma cells, induced by the Dacron fibers.

Table 3 - *Indications and Contra-Indications.*

ESSURE can be a true alternative for
A woman who wants definitive sterilization and complies with the family planning criteria - older than 25 years or has two children – as defined by Law No. 9263;
A woman that has experienced adverse effects with other contraceptive methods;
Healthy patient with the possibility of obstetrical problems in a future pregnancy;
Patients with comorbidities (hypertension, diabetes, heart disease, obesity, Down Syndrome, etc.) and;
A woman who does not want to subject herself to the risks of anesthesia and surgery, with their possible complications.
Patients who cannot use this method
Women who do not meet the prerequisites of Law No. 9263;Uncertainty about definitive sterilization;
Suspicion of pregnancy;
Is within six weeks of a delivery or abortion;
Recent or current acute pelvic infection;
Untreated acute cervicitis;
Metrorrhagia of unknown etiology;
Suspected or known gynecologic neoplasia;
Abnormal uterine cavity or Fallopian tubes and;
Patients using corticosteroids.

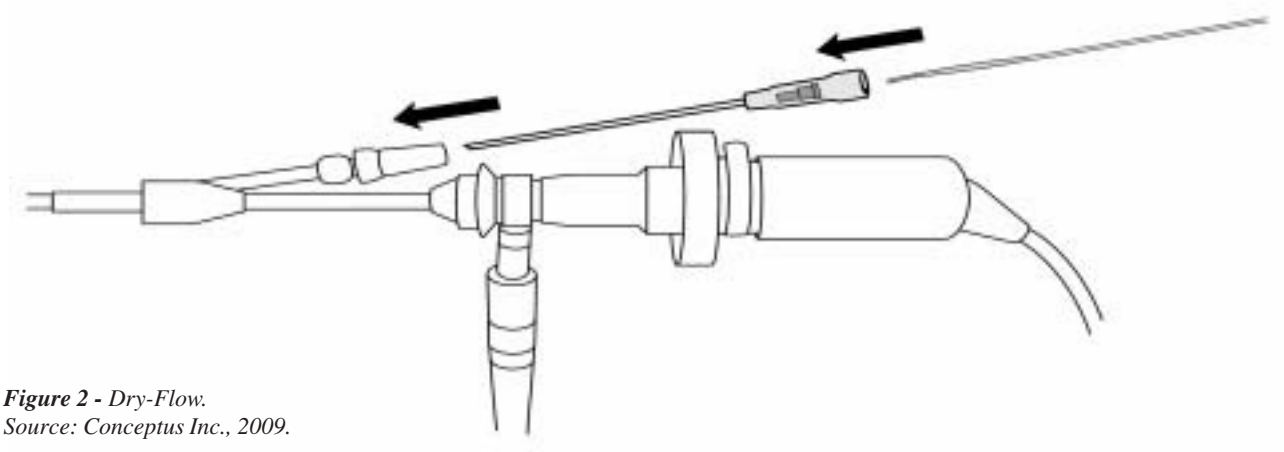

Figure 2 - *Dry-Flow.*
Source: Conceptus Inc., 2009.

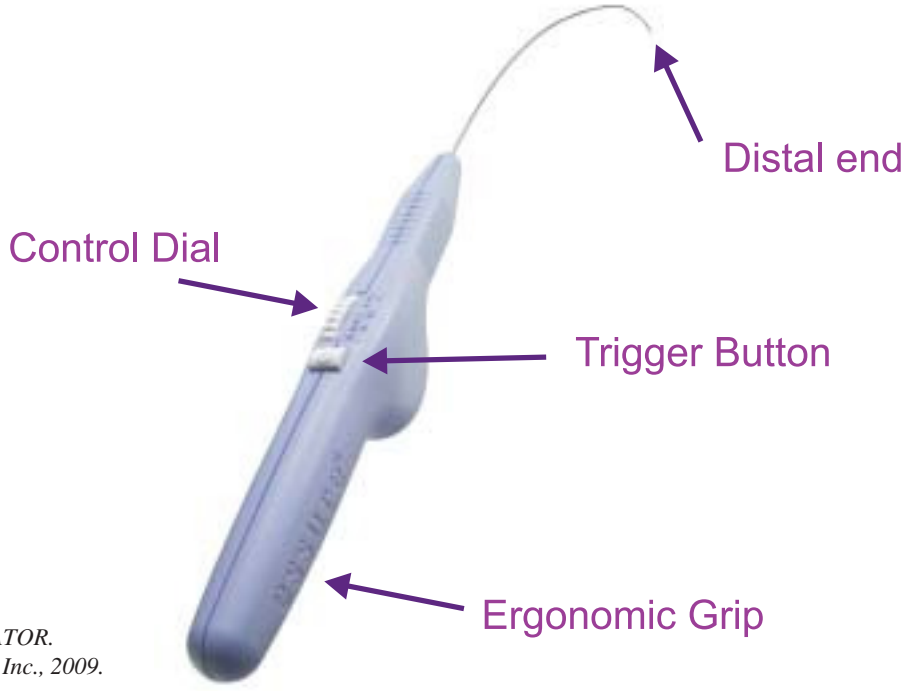

Figure 3 - *APLICATOR.*
Source: Conceptus Inc., 2009.

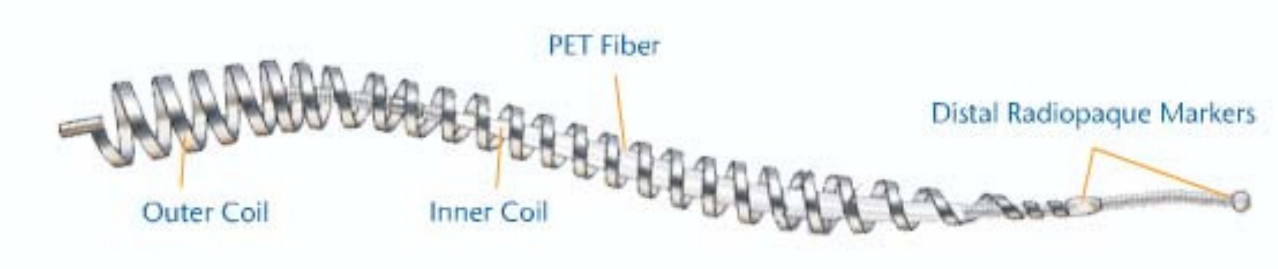

Figure 4 - *MICRODEVICE.*
Source: Conceptus Inc., 2009.

INDICATION AND CONTRA-INDICATIONS FOR THE PROCEDURE ARE STED IN TABLE 3

The placement of ESSURE should be performed during the first phase of the menstrual cycle, due to the more certain identification of the tubal ostia and the lower risk of inserting a device in a pregnant patient.

The prior use of an OCP permits the placement during any day of the cycle.

The use of a non-steroidal anti-inflammatory drug (NSAID) one hour before the procedure – administered orally or rectally – diminished uterine contractions and pain. Similarly the use of benzodiazepines (for example: 10mg diazepam given orally) reduced anxiety.

INSERTION

The advantages of the ESSURE system include the fact that it can be inserted in an outpatient setting, eliminates incisions, and does not require anesthesia. The patient is discharged after placement of the microdevice and can return to their normal work activities the same day.

For ESSURE placement a hysteroscope with an operative canal – such as equipment developed by Bettocchi – is necessary. The equipment has a oval format, with an anteroposterior dimension of 5 mm and a transverse dimension of 3.9 mm. The dry-flow introducer is first placed in the work canal of the hysteroscope; the introducer has an antireflux valve that maintains the intrauterine pressure and at the same time protects the distal part of the microdevice. The ESSURE system is guided to the tubal ostium by the introduction catheter with the proximal segment of the tube catheterized up to the black mark of the catheter. The control dial on the handle is rotated back until it locks, whereupon the outer covering of the catheter retracts displaying the gold marking that should be positioned at the opening of the ostium. At this time the trigger button is fired, and the dial is again rotated until it locks, in order to expand and disconnect the microdevice. At this point, the entire system is removed revealing the spirals in the interior of the uterus. In a good placement, there should be three to eight spirals. Repeat the procedure in the contralateral tube. A recent study demonstrated a successful rate of 99.8% ([4]).

Analyzing 1615 women who had undergone insertion of ESSURE and were premedicated with ibuprofen and oral benzodiazepines, Arjona and cols.[4] reported that 86.5% considered it "excellent" or "very good"; 10.2% felt pain similar to menstruation, and considered their ability to tolerate the placement as "good"; and only 3.1% considered it "average" or "poor," feeling pain that was stronger than their menstrual pain. Time to return to normal activities was less than a day for 75.8%, one day for 21.3%, and more than one day for 2.9%. The degree of satisfaction with the method varied from 96.0% to 99.9%.

Duffy and cols.[6] , compared ESSURE with laparoscopic sterilization regarding pain and found double the tolerance ("good" to "excellent") for the process of inserting ESSURE.

EXAMES POST-INSERTION DO ESSURE

It is necessary to use alternative contraceptive methods for at least three months after placement of the microdevice. Various studies in the EUA have demonstrated follow-up rates post-insertion of ESSURE that varied from 13% to 95%, depending on the education level of the patient, the medical counseling, as well as the adherence to these recommendations.[5] For post-insertion monitoring of ESSURE in the United States, the CDC requires that a hysterosalpingogram (HSG) be performed after three months to confirm the effectives of the method (Figure 5). Worldwide studies, however, have shown

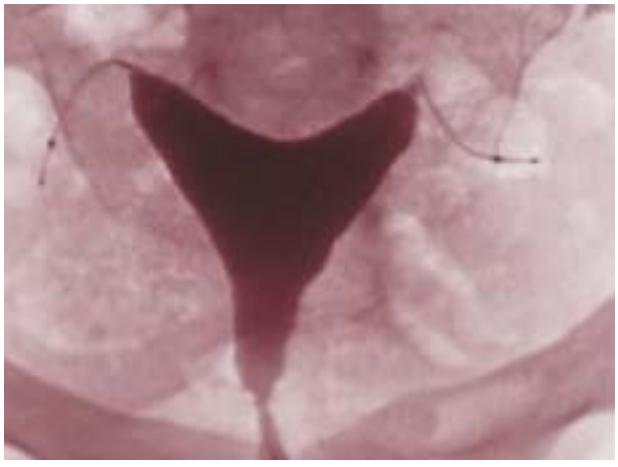

Figure 5 - *Hysterosalpingogram (HSG) after insertion of ESSURE. Source: Conceptus Inc. 2009.*

that the microdevice is well visualized by simple radiographs of the pelvis.[7]

Veersema and cols., analyzing 150 patients, concluded that the hysterosalpingogram typically performed three months after ESSURE placement could be replaced with a transvaginal ultrasound (TVUS), which is better accepted by the patient and is less expensive.[8] Kerin and Levy also validated TVUS, reserving hysterosalpingograms for atypical cases.[9]

In clinical trials, ESSURE achieved tubal occlusion in 96% of cases after three months. When this did not occur, it was recommended that patient wait as additional three months before obtaining another hysterosalpingogram (HSG); at six months tubal occlusion was 99.8%.[10]

Although several studies indicate that localization of the microdevice by transvaginal ultrasound procedure is simple and reliable in most patients, it is not part of the manufacturer's protocol. Given that the patient signs an informed consent document that outlines what should be done post-insertion, it is hard to deviate from that guidance.

RESULTS

The CREST study showed that in terms of effectiveness transcervical tubal occlusion was second only to monopolar cauterization of the Fallopian tubes, but after waiting 12 weeks to perform a hysterosalpingogram (HSG) to confirm the tubal obstruction, its effectiveness rose to 99.8%.[2]

Kerin, analyzing 37 pregnancies reported by the manufacturer that occurred between 1997 and 2004, found that six women (16%) were pregnant before the placement of the device, seven (19%) had hysterosalpingograms that were misinterpreted, and 21 (57%) had not followed the post-insertion protocol.[11] The author concluded that the majority of these pregnancies could have been avoided by placing the device during the first phase of menstrual cycle, continuing to take an OCP for several months, ensuring more accurate hysterosalpingogram results, and by strict observance of the post-insertion protocol. Levy, evaluating 50,000 procedures through December 2005 obtained results quite close to the prior studies, as shown in Table 4.[7]

Although the use of ESSURE precludes the intra-uterine device (IUD) as a temporary form of contraception, the microdevice can be placed in the presence of an IUD. In a series of 28 patients, Connor needed to remove eight IUDs (28.6%) for the proper positioning of ESSURE bilaterally; of the remaining twenty patients, 19 insertions were considered easy and one difficult.[12]

Endometrial ablation is the other procedure that can be associated with ESSURE placement, since fertile women can conceive after ablation (about 1.5%) and, of these, only 13% were absolutely normal pregnancies.[13] Follow-up three months after ESSURE placement with concomitant endometrial ablation was hampered by adhesions. The manufacturer recommends ablation after a period of three months and confirmation of tubal obstruction. Connor recommends concomitant ablation with ESSURE placement, as long as transvaginal ultrasound (TVUS) is used as a control.[14]

COMPLICATIONS

With regard to safety, a pilot study with 745 women enrolled between 1998 and 2001 showed no complications of major consequence, such as intestinal or vascular lesions or death. However, tubal perforation was observed in 2.3% of cases, though none of these evolved into significant complications.[15]

The studies found that there were no cases of pelvic inflammatory disease after placement of the

Table 4 - *Causes of pregnancy reported.*

Reason for the pregnancy	N	% of the Total
Physician or Patient did not follow the protocols	30	47
Plain radiograph of the pelvis or hysterosalpingogram (HSG) poorly interpreted	18	28
Pregnant at the time of placement	8	12.5
Defective Microdevice	1	1.5
Other	7	11
Total	64	

Table 5 - *Causes of pelvic pain after ESSURE placement.*

Device poorly positioned, including the intra-abdominal placements, excluding hysteroscopic perforations.	5
Endometrial ablation with concomitant monopolar or bipolar current, Thermachoice, NovaSure, including infection.	4
Unilateral or bilateral angular perforation.	5
More than one microdevice placed in 1 or 2 Fallopian tubes.	2
Unknown	6

microdevice. A vagal reflex occurred in about 1% of cases. The microdevice migrated into the abdominal cavity in 0.1% of cases and was expelled in 0.7%.[12]

A review by the FDA of the MAUDE (Manufacturer and User Facility Device Experience) database since the introduction of ESSURE in 2002 through 2009 found three reports of uterine perforation, with incorporation of the micro device in abdominal structures which required removal.[16] Connor [12] consulted the MAUDE database for period from 2004 to 2009 and found 22 cases of pelvic pain that required treatment (Table 5). Besides this, for the same period, the author verified five pregnancies after placement of ESSURE, of which four were in the first year after placement. One of the women with an ectopic pregnancy did not use contraception in the three months post-insertion. A second was recognized when her hysterosalpingogram revealed incorrect positioning (too proximal), a third did not have hysterosalpingogram results, and the fourth did not obtain a hysterosalpingogram.

Although it does not constitute a contraindication, the presence of an IUD increases the degree of difficulty of inserting the microdevice ([4]).

COSTS

The outpatient nature of ESSURE placement enables this method of contraception to be offered at an affordable price. Connor showed a reduction of $180 dollars per patient for procedures performed in surgical centers and a reduction of $2075 when laparoscopic sterilization was compared with outpatient ESSURE placement.[12]

FINAL CONSIDERATIONS

The ESSURE microdevice is a method of definitive female contraception that is minimally invasive, safe, and effective. It presents low rates of adverse effects and has a competitive cost-benefit ratio, when compared with other minimally invasive methods.

RESUMO

O controle da natalidade é uma necessidade da sociedade. Os métodos anticoncepcionais facilitam o planejamento familiar. O anticoncepcional oral (ACO) é o método temporário mais utilizado. A esterilização feminina é um método de anticoncepção definitiva. As vias de acesso cirúrgico para esterilização feminina incluem a laparotomia e as técnicas minimamente invasivas, como a laparoscopia (laparoscopy) para a ligadura das tubas (LT) e a oclusão tubária por microdispositivos (ESSURE e ADIANA), guiados por histeroscopia (HSC), cujas principais vantagens são: colocação ambulatorial, ausência de incisões ou de anestesia. O ESSURE é composto de aço inoxidável, dacron e nitinol. Seu mecanismo de ação se dá pela produção de reação fibrosa local, sendo indicado para mulheres que estão seguras quanto à realização de esterilização definitiva, beneficiando sobremaneira as que apresentam comorbidades, com risco cirúrgico elevado. É contra-indicado em doença inflamatória pélvica, uso de corticoesteróides e sangramento uterino anormal. Outros métodos anticonceptivos devem ser utilizados nos três primeiros meses após a inserção do microdispositivo, quando se realiza exames complementares, such as hysterosalpingogram (HSG), plain radiographs (X-ray) or ultrasound (US), the purpose of confirming tubal occlusion. com o objetivo de identificar a oclusão tubária. O method atinge 99,8% de eficácia. As complicações mais comuns são a expulsão do microdevice e a perfuração útero-tubária. Os custos são semelhantes aos da ligadura das tubas por laparoscopy e a curva de aprendizado é pequena.

Palavras-chave: Esterilização tubária, Histeroscopia, Microdispositivo Intratubario, Contracepção permanente.

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Brazilian Journal of Videoendoscopic Surgery

Case Report

Abdominal Compartment Syndrome and Pulmonary Edema in Hysteroscopy Resection of Uterine Septum

Síndrome do Compartimento Abdominal e Edema Pulmonar na Ressecção Histeroscópica do Septo Uterino

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ABSTRACT

The case is a 37-year old woman scheduled for resection of uterine septum by hysteroscopy. The occurrence of two complications of hysteroscopy, the fluid overload and abdominal compartment syndrome simultaneously in our patient led to a catastrophic outcome.

Key words: Hysteroscopy; Abdominal compartment syndrome; pulmonary edema.

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CASE REPORT

A 37-years-old woman, 72 kg, with history of infertility presented for resection of uterine septum by hysteroscopy. Her medical history and lab data were unremarkable. After the induction of anesthesia using Sufentanil 10 mg, sodium thiopental 300 mg, intubation was facilitated with 25 mg Atracurium. Anesthesia was maintained with Isoflurane in 50% oxygen and air. Hysteroscopy began with normal saline as distention media. The surgeon, however, used laparoscopic pump for hysteroscopy and up to 10 liters saline as irrigation fluid. Blood pressure and pulse rate suddenly dropped 15-20 minutes after surgery started (BP: 75/40 mmHg and PR: 30 beat/min). Atropine 0.5 mg was infused immediately and the surgeon was informed about the problem. Vital signs became stable temporarily but only after some minutes typical signs of compartment syndrome consisting of severe abdominal distention, severe bradycardia and hypotension, engorgement of cervical vein, congestion of face, increased airway pressure and cyanosis were developed. Even blood rushed out of the two IV catheters of the patient. She developed cardiac arrest and resuscitation promptly started.

We asked the surgeon to open the abdomen. Laparotomy and suction of fluid resulted in immediate improvement and the sinus rhythm was back again. Furosemide was administrated and a urine catheter was placed. However, pulmonary edema developed soon and a large amount of clear fluid repeatedly came out of the tracheal tube. The patient was unstable and required resuscitation frequently. She received epinephrine, atropine sodium bicarbonate, dexametasone and a large amount of furosemide. After 1.5 hours the patient was admitted to ICU with sinus rhythm, spontaneous ventilation, spo2 94%, blood pressure 94/53 mmHg, pulse rate 115 beat/min and good diuresis. Her pupil was dilated and minimally reactive to light. Blood analysis revealed: Na=156 mmol/l K=3.2 mmol/l Ca=6.1 PT=22 PTT=68 INR=2.7 Alb=2.1. In ICU the patient received full ventilatory support and was given thiopental drip, morphine and dexamethasone as aid to brain protection. She also received furosemide and epinephrine infusion. Several hours later her pupil size became normal and reactive to light and after 24 hours she opened her eyes on command. Laboratory data became normal but in spite of several medication and expert consultation she was still suffering from pulmonary edema. At last, 30 hours after surgery O2 saturation deteriorate, blood pressure dropped and she developed ventricular fibrillation and cardiac arrest and was finally pronounced dead after 2 hours of

resuscitation. The patient family refused to allow an autopsy to be performed.

DISCUSSION

Compartment syndrome is a rare complication of hysteroscopy. Volume overload is another complication that might develop by a variety of mechanisms such as absorption across endometrium, intravasation through surgically opened venous channel and spill from fallopian tube with absorption by the peritoneum (1) . Excessive intravasation may lead to fluid overload, congestive heart failure, pulmonary edema, electrolyte imbalance and dilutional coagulopathy (2,3). Different types of distention media used in hysteroscopy include saline, low viscous fluid such as sorbitol, manitol and glycine solutions and carbon dioxide, each with its distinct advantages or limitations.

In our case, saline was used as distention media (10 liter/ 20 min). In addition to large volume of fluid, laparoscopic pump rather than hysteroscopic pump was used. It is important to note that due to lack of hysterescopic pump at our medical center, laparoscopic pump was wrongly used. When working in a narrow cavity such as uterine, it is obvious that the exact management of the pressure is essential. If intrauterine pressure became greater than the patient mean arterial pressure, intravasation of distending media into the vascular system can occur, in a way that high intrauterine pressure can result in increased absorption of distention media and volume overload (4).

Uterine perforation can occur during any operative hysteroscopy procedure but it is most common during septum resection, myomectomy and lysis of synechia (5). Autopsy was not conducted to see if there has been any uterine perforation in our case. The maximum fluid patients can tolerate is not obvious and it will depend on age, weight and cardiovascular status. Normal saline 0.9% can be tolerated better than other distention media and hyponatremia will not be a problem(6).

There are many case reports on hysteroscopy complications (7,8,9). Hyponatremia is a common laboratory test in volume overload. However, in our case hypernatremia was a problem, even though absorption of saline per se could not explain hypernatremia. Rapid infusion of saline predictably resulted in hyperchloremic acidosis (10,11,12). On the other hand, the patient suffered metabolic acidosis due to cardiac arrest; so the need to sodium bicarbonate in order to manage acidosis was increased and resulted in hypernatremia.

Usually one of the most common signs of volume overload is hypertension but our patient did not develop any episode of hypertension. In fact, signs of compartment syndrome masked the sign of volume overload and the simultaneous occurrence of two complications of hysteroscopy in a patient led to a catastrophic outcome. Surgeons and anesthesiologists must be familiar with and aware of complications of hysteroscopy and observe safety points. Experience and skills of surgeons is also an important factor preventing similar events.

RESUMO

O caso se refere a uma mulher de 37 anos submetida à ressecção de septo uterino por histeroscopia. A ocorrência simultânea em nossa paciente de duas complicações da histeroscopia, o excesso de fluido e a síndrome compartimental abdominal, levou a um desfecho catastrófico.

Palavras-chave: Histeroscopia; síndrome compartimental abdominal, edema pulmonar.

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INFORMATION FOR AUTHORS

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- Manuscripts should be printable on one side of a 216x279mm or A4(212x297mm) white sulphite paper with margins of 25mm.
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- Abstract/Key words;
- Text pages and Acknowledgments;
- References;
- Tables (one in each page, separately);
- Illustrations;
- Legends;
- Abbreviations.

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- Complete Manuscript Title(concise and informative)
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June 12-16,2011
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Website:www2.kenes.com/was2011/Pages/Home.aspx

4th International Urolithiasis Research Symposium
Indianapolis, In,USA
June 16-17, 2011
E-mail: csprunger@clarin.org
Website: www.iksi.org/index.php/stone_conference/program

Cancer Survivorship and Sexual Health Symposium SMSNA& ISSM
Washington D.C.,USA
June 17-19,2011
E-mail: offi ce@issm.info
Website:www. cancersurvivosandsex.org

Brachytherapy for Prostate Cancer
Poznan, Poland
June 26 -28, 2011
E-mail: education@estro.org
Website:www.estro-education.org

Annual Meeting International Urogynecological Association
Lisboa, Portugal
June 28 – July 2, 2011
E-mail:Office@iuga.org
Website: www.iuga.org

27th Annual Meeting European Society of Human Reproduction & Embrology
Stockholm, Sweden
July 3 – 6, 2011
E-mail: videourology2011@symposiacongressi.com
Website: www.symposiacongressi.com

Video Urology 22 and World Congress 2011
Torino, Italy
July 7 – 9, 2011
E-mail: videourology2011@symposiacongressi.com
Website: www.symposiacongressi.com

ESU – Weill Cornell Masterclass in Urology
Salzburg, Autria
July 10 -16, 2011
E-mail: seu@uroweb.org
Website: www.eusalzburg.uroweb.org/

6th Biennial Meeting of Asia Pacif Society for the of Aging Male (APSSAM)
Busan, South Korea
September 1 – 4, 2011
E-mail: secretariat@apssam2011.org
Website: www.apssam2011.org/

9th European Urology Residents Education Programme (EUREP)
Prague, Czech Republic
September 2 – 7, 2011
E-mail: J.mcgrath@congressconsultants.com
Wesite:www:eurep.uroweb.org

41st National Congresso f the Poilish Association of Urology
Gdansk, Poland
Septermber 8 – 10, 2011
E-mai: kongresptu@ptu.net.pl
Website: www:pturol.org.pl/

ESU organised course at the time of the national congresso of the Polish Association of Urology
Gdansk. Poland
September 9, 2011
E-mail: seu@uroweb.og
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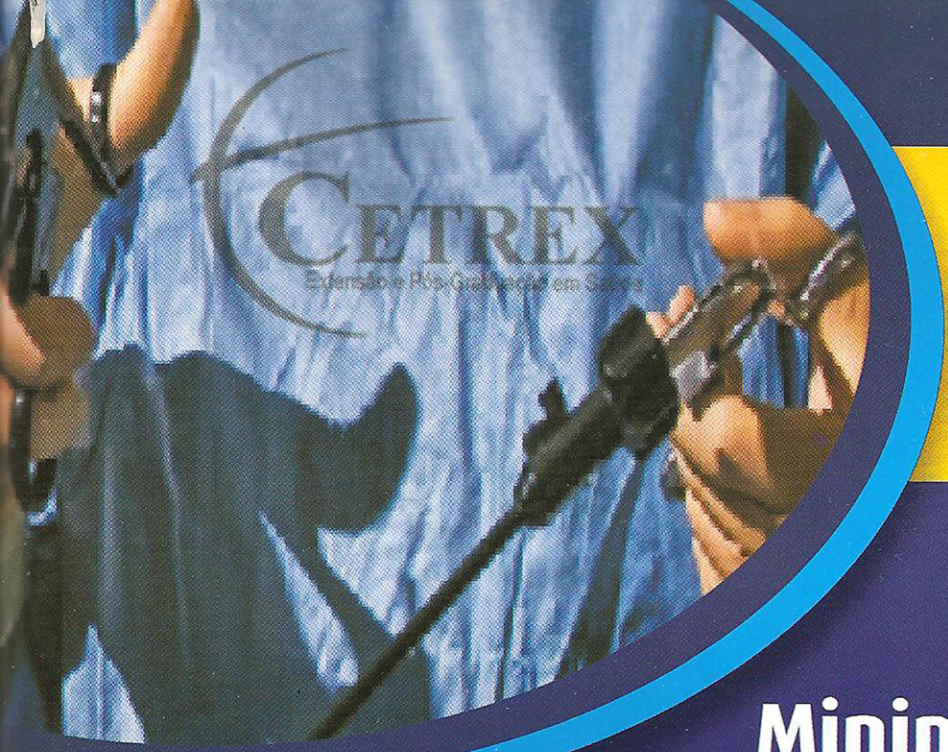

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