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CRITICAL APPRAISAL OF SURGICAL THESES ON PORTAL HYPERTENSION.

By
Nabil Dowidar, MChAlex, DrChAlex
Department of Clinical and Experimental Surgery, Medical Research Institute, University of Alexandria, Egypt

Background: *There are few local guidelines on the management of patients with oesophageal varices secondary to schistosomal hepatic fibrosis. The study aims at exploring this issue through a critical appraisal of the methodology used in surgical theses on portal hypertension.*

Material and methods: *All surgical theses on portal hypertension, written over a 27-year period were analyzed through established criteria for evaluating research on portal hypertension.*

Results: *Study design analysis revealed that 90% theses were case series reports and 10% were randomized clinical trials. Control of bleeding and patient survival were primary research end points in 30% and 25% of the theses, respectively. None of the theses had the number of patients required for their study statistically calculated beforehand. Patient population was defined in 30% of the theses and was heterogeneous in 50% of the theses; mixing bleeders with non-bleeders. Child-Pugh grading was followed in 15% of the theses. Endoscopic variceal grading was performed in 55% of the theses and in 10% were endoscopic risk signs for bleeding reported.*

Conclusion: *This study has demonstrated the need for well-designed clinical trials on portal hypertension that have end points of primary importance, such as patient survival and control of bleeding.*

Keywords: *Hypertension, portal – esophageal and gastric varices - hematemesis – methods – clinical trials*

INTRODUCTION

Oesophageal varices secondary to liver disease are one of Egypt's main health problems. Schistosomiasis and viral infections are the two main causes for the wide spread of liver disease in Egypt.[1] Although, benign in nature, liver disease acquires a malignant course with the development of portal hypertension and its associated varices in the lower oesophagus. When ruptured, these relatively small veins can lead to the loss of considerable amounts of blood. In Egypt, a third of patients who are admitted to hospital because of variceal bleeding die and if they survive their first bleed are under the constant threat of recurrent bleeding, which carries a greater mortality risk.[2]

Over the last two decades, diagnostic approaches and therapeutic modalities for patients with oesophageal varices have changed dramatically. For example, on the diagnostic end, endoscopy and ultrasonographic examination have extended the capability of doctors in evaluating oesophageal varices[3] and studying the liver.[4] On the therapeutic end, pharmacological agents (vasoactive agents, β-blockers),[5] endoscopy,[6] and the rediscovery of shunt procedures whether performed surgically[7] or through intervention radiology (TIPSS)[8] have changed the management of variceal bleeding dramatically.

However, the value of each diagnostic approach and proper place for each therapeutic modality is still not clear.[9] This becomes even more complex when the desired effect from treatment is considered which could be the

arrest of active bleeding, or the prevention of first bleeding (primary prophylaxis), or the prevention of rebleeding (secondary prophylaxis). For these reasons, many protocols have been proposed and studies performed in an attempt to pin point the most appropriate therapy for patients with oesophageal varices.

The aim of this work is to assess whether surgical theses on portal hypertension have addressed this problem adequately and whether the theses were performed using uniform nomenclature and definitions, well-defined parameters for assessment, and adhered to established methods of research.

PATIENTS AND METHODS

All theses written on portal hypertension and submitted to the Department of Surgery, Faculty of Medicine, University of Alexandria in partial fulfillment of the requirements of the degree of doctor of surgery and successfully defended before the end of 1998 were included.

A detailed data sheet was prepared following established criteria for the evaluation of research and clinical trials in portal hypertension.[10] The sheet was completed as each thesis was studied. The sheet covered the following items: thesis design, thesis aim, sample size, patient population (definition, inclusion and exclusion criteria), use of control, post-mortem, use of animals, treatment evaluated, liver biopsy, portal haemodynamics, Child[11] or Child-Pugh[12] grading, hepatitis markers, variceal grading, endoscopic risk signs for bleeding,[13,14 ,15] follow-up, state of lost patients, and recommendations for other or larger studies.

RESULTS

Twenty theses, written between 1964 and 1991, fulfilled the selection criteria. Study design analysis of each thesis revealed that 18 (90%) theses were case series reports and only two (10%) were randomized clinical trials. The different aims of the theses are shown in Table I. Control of bleeding and patient survival were covered in only six (30%) and five (25%) theses, respectively. The sample size and patient population criteria of the theses studied are shown in Table II. None of the theses had the number of patients required for their study (sample size) statistically calculated beforehand. The median (min-max) number of patients per thesis was 57.5 (17-278). Six (30%) theses only defined their patient population and in all were defined by patient admittance to a surgical unit. Ten (50%) theses included a heterogeneous patient population i.e. a mixture of bleeders and non-bleeders, while only six (30%) theses included a homogenous patient population of bleeders. Four (20%) theses did not mention the nature of their patient population as regards bleeding. Inclusion criteria were defined in 19 (95%) theses, however, 3 (15%) theses only defined their exclusion criteria and this was for patients with ascites and liver dysfunction. Only one of the three theses defined the degree of liver dysfunction used to exclude patients from entering their study. However, the number of excluded patients was not mentioned in any of the theses. None of the theses mentioned either the time lapse from initial diagnosis of varices or the time lapse from index bleed to entry into the study. Two theses (10%) used post-mortem studies to verify some of their findings and only one (5%) thesis used animal experiments as part of its study design.

The therapeutic modalities evaluated and the number of patients enrolled into each modality are listed in Table III. A total number of 1335 patients were included in the twenty theses, 1123 (84%) patients received surgical therapy, 122 (9%) patients were used as control and 90 (7%) patients received endoscopic therapy (non-surgical).

Measures taken to evaluate liver function and grading of varices in each thesis are shown in Table IV. All liver biopsies were taken during surgery. None of the patients, in any of the theses, was serologically tested for past infection with hepatitis B or C virus. Three (15%) theses only used well-defined parameters for liver function assessment (Child-Pugh grading). The varices were graded endoscopically in 11 (55%) theses, and in only two (10%) were endoscopic risk signs for bleeding reported. Seven theses (35%) did not use any form of evaluation for the presence or absence of oesophageal varices.

Twelve (60%) theses presented their follow-up results but only three mentioned the number of patients lost during the follow-up period. Six (30%) theses recommended the conduction of other studies in view of their findings. However, none recommended the need for larger studies to further verify their initial findings statistically.

Table I: ***Aims of theses****

Aim	*No. of studies (%)*
Gastrointestinal function	10 (50)
Variceal bleeding	6 (30)
Portal haemodynamics	6 (30)
Survival	5 (25)
Ascites treatment	5 (25)
Variceal characters	3 (15)
Thoracic duct characters	3 (15)
Decision-making	3 (15)
Omentum	1 (5)
Respiratory function	1 (5)
Compliance with treatment	1 (5)
Not clear	1 (5)

* Each thesis may have more than one aim

Table II: ***Sample size and patient population.***

Item	*No. of studies (%)*
Sample size	
Statistically calculated	0 (0)
No. of patients < 25	2 (10)
No. of patients between 25-50*	6 (30)
No. of patients between 51-75*	7 (35)
No. of patients between 76-100	3 (15)
No. of patients > 100	2 (10)
Patient population	
Defined	6 (30)
Inclusion criteria defined	19 (95)
Exclusion criteria defined	3 (15)
Time lapse from index bleed	0 (0)

* Number of clinical trials = 1

Table III: ***Treatment evaluated.***

Treatment	*No. of theses (%)*	*No. of patients*
Devascularisation	18 (90)	1051
Control patients	7 (35)	122
Endoscopic treatment	3 (15)	90
Selective shunt	3 (15)	60
Total shunt	3 (15)	12

Table IV: ***Liver and varices evaluation.***

Item	*No. of studies (%)*
Liver biopsy	18 (90)
Portal haemodynamic evaluation	14 (70)
Child-Pugh grading	3 (15)
Hepatitis markers	0 (0)
Variceal grading	
Via endoscopy	11 (55)
Endoscopic risk signs	2 (10)
Via barium swallow only	2 (10)

Table V: ***Number of patients required in a clinical trial aimed at demonstrating an increase in control of bleeding.****

% control of bleeding with current treatment	*% increase in control of bleeding with new treatment*			
	75%	***80%***	***85%***	***90%***
65% control of bleeding	696	302	164	100
70% control of bleeding	2580	626	266	142

* Type I error = 5% - Type II error = 20%

Table VI: ***Parameters for a clinical trial .***

Item
Aims (end points)
Stop active bleeding, or prevent first bleeding, or prevent rebleeding
Survival analysis
Patient characteristics
Population identification
Inclusion and exclusion criteria, and number of patients excluded
Bleeding
Definition of a bleeding episode and its separation from another episode
Definition of variceal bleeding and non-variceal bleeding
Number of patients actively bleeding at time of entry into the study
Liver characteristics
Child-Pugh grade (albumin, bilirubin, prothrombin, ascites, encephalopathy)
Hepatitis markers
Endoscopic appearance of varices
Size, colour, risk signs, gastric varices
Treatment outome
Complications
Criteria of success and failure
Statistical considerations
Sample size calculation
End point definition

DISCUSSION

This study has demonstrated a great need for a consensus on the appropriate definitions, methodology and therapeutic modalities to be used in future research on portal hypertension. There is a general lack of adherence to established methods of research, study planning and statistical analysis. The theses studied differ greatly, especially in the way information about patients and methods used is reported, making interpretation of their results and placing them in the context of each other and other work difficult. This is a situation, which leads to conflicting and sometimes false conclusions.

The theses studied, which present surgical research on portal hypertension over a 27-year period, do not in any way evaluate surgical therapy in comparison to other modalities. Most theses (90%) written were case series reports which at their best can only describe treatment outcome in a numerical fashion (estimates of outcome). In other words, they can not inform us if a particular treatment is superior to another or not. To be able to evaluate a particular treatment, a randomized clinical trial should be conducted where a particular treatment e.g. surgery is compared to another e.g. endoscopy or to no treatment e.g. non-specific supportive therapy.[16,17] Clinical trials constituted only 10% of the theses written, which explains why doctors find great difficulty in deciding on the appropriate therapeutic modality which best suites their patient. Case series reports are not necessarily inferior to clinical trials or other forms of research; they are important as their results, in many circumstances, are used to define problem areas worthy of future clinical trials and research.

The core of any research is its aim (end point) and should, in the first place, be directed towards answering questions that are of primary importance to the well-being of the patient. In portal hypertension, bleeding and survival are the two end points which are of primary importance and research should be targeted towards finding the treatment which best achieves them.[18] Research areas such as gastrointestinal function or thoracic duct characteristics are of secondary importance and may even be clinically irrelevant. Furthermore, these topics can be easily covered while tackling points of primary importance. In only 30% of the theses written was the research specifically aimed at points of primary importance.

Researchers should also be clear about whether they are aiming at primary or secondary prophylaxis of bleeding from oesophageal varices and should not mix patients from both groups in one study as evident in 50% of the theses examined. The justification for treatment of non-bleeders is totally different from that of bleeders. In the former group, the aim is to lower a hypothetical risk of the first bleed and an aggressive approach with a relatively high morbidity and mortality is not justified with primary prophylaxis as with secondary prophylaxis.[19]

A crucial point, that should never be ignored, when planning a study, is the number of patients that needs to be enrolled into the study to make its results valid. Enrolling too few patients will give insignificant results, as little data will be available to give statistical power to the study.[20,21] On the other hand, enrolling too many patients may unnecessarily expose patients to a potentially harmful treatment. In both situations, time and effort will be lost, not mentioning the frustrations and loss of resources. None of the theses had their sample size statistically calculated beforehand, thus making their results difficult to interpret.

The sample size of any study can be calculated with the help of specially constructed formulas. It is advisable to consult a statistical expert, to help in the calculation of the sample size before embarking on a clinical trial. Nevertheless, simple nomograms are available that can easily be used to supply any researcher with the appropriate number of patients required.[22] In the situation of a clinical trial, where one therapy is compared to another, the number of patients required is based on the results of the current treatment and the expected benefit from endorsing the new treatment. A good idea of how many patients are required to run a clinical trial can be obtained from Table V. It should be noted that there are special nomograms for the calculation of the number of patients required for clinical trials where its main end-point is survival analysis.[23]

For its results to be valid, surgical research has to be conducted on patients who represent the real-life situation i.e. wider patient population. If one defines a study population that is in a better condition than the wider patient population, then the claimed benefits of this research will never be reproduced when widely applied. Patient population was defined only in 30% of the theses written and was conditioned by admission to a surgical unit i.e. the patient was fit to undergo surgery. This immediately creates a selection bias towards the inclusion of patients who belong to the fit end of the spectrum and this by itself will lead to false good results.[24] Another point which adds bias is the exclusion of patients who belong to the unfit end of the spectrum. It is permissible to exclude patients who are unfit from a study, especially if the treatment involved presents a certain risk to their well-being. However, it is not permissible not to report this exclusion and not to mention the number of excluded patients. Exclusion criteria were only defined in 15% of the theses written and in none was the number of excluded patients mentioned.

Another point that can produce bias especially with case series reports, is the time lapse from active bleeding to entry into a study.[25] Patients who are bleeding or who had just had their bleeding controlled are more liable to develop complications, some fatal, than patients who have survived their bleeding episode and are physically active when enrolled into a study. Researchers have to report on this period, as it will help fellow researchers interpret their results and understand the circumstances in which they were produced. None of the theses written reported on the time lapse from active bleeding to study enrollment.

The results from research on liver disease, regardless of its etiology, are usually presented in relation to its function. Most researchers nowadays use the Child-Pugh grading system[12] in their reporting as the results significantly differ between its three classes.[26] Only 15% of the theses written endorsed such an approach, which makes the interpretation of the results of the other theses difficult, if not impossible. Furthermore, it annuls the possibility of comparison between the theses or with research done elsewhere on totally different patient populations.

It is difficult to imagine performing research on portal hypertension without confirming the presence of varices. However, in 35% of the theses written no attempt was made to confirm their presence. Although the availability of flexible endoscopy has eased the task, most theses (90%) did not report on endoscopic risk signs for variceal bleeding. Differences in bleeding rates from one study group to another could simply be the result of the unequal distribution of patients with varices that are at a greater risk of bleeding.[27]

The lack of uniformity in reporting clinical data creates great difficulty in evaluating clinical research and in many circumstances may lead to its repetition. This study has demonstrated the great need to unify research on portal hypertension by using well-established methods when conducting the research.[28] There is a cry for soundly designed clinical trials, which have aims of primary importance and which are conducted on a well-defined and calculated patient population, with predetermined clinical parameters to report on. The minimum of parameters, which should be available in a clinical trial on portal hypertension, are shown in Table VI. These parameters do not only ensure the validity of the trial results but also permits comparison of data and its cumulative analysis after many years of research. When such evidence-based research becomes available, doctors will no longer face a dilemma when deciding on the definitive treatment of a patient with bleeding oesophageal varices.

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