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Long-term outcome after partial splenectomy compared to total splenectomy in children with spherocytosis

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A B S T R A C T

Splenectomy may be required for Hereditary Spherocytosis (HS) management. The severe infection risk after total splenectomy (TS) has led to an increasing interest in partial splenectomy (PS). Previous studies suspected that PS may be less effective, but long-term studies are lacking. Here, we compared the long-term efficacy of TS and PS.

This French national multicenter retrospective study (2005–2017) included 96 children with a minimum post-surgery follow-up of 5 years. The primary endpoint was the hemoglobin concentration at the follow-up end. Intra- and post-operative complications and **completion splenectomy were also reported**.

TS was performed in 70 patients (72.9 %) and PS in 26. The mean post-surgery follow-up was 8 years (5–17). At the follow-up end, **hemoglobin** concentration was significantly higher in the TS than PS group (13.86 g/dl ± 1.74 vs 11.87 g/dl ± 1.28, $p < 0.01$). Postoperative complications **were not** different, but hospital stay was longer for PS (6.9 ± 2.6 days vs 4.9 ± 2.5 days, $p < 0.01$). Following PS, **completion splenectomy** was required in 11/26 patients (42.3 %) after a mean interval of 7 years (first 8 years after PS for 25 % of patients and after 17 years for one patient). Hemoglobin concentration was 11.8 g/dl ± 1.28 after PS and 14.49 g/dl ± 1.34 ($p < 0.01$) after completion splenectomy, similar to that in the TS group. Hemoglobin concentration <8.5 g/dL was a risk factor of later **completion splenectomy** (OR = 10; 95 % CI [2.23–100]; $p = 0.03$).

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PS is associated with lower hemoglobin concentration and a significant risk of **completion splenectomy** several years after the initial surgery. Therefore, it requires long-term hemoglobin concentration monitoring, especially if the pre-surgery value is < 8.5 g/dL.

1. Introduction

Hereditary Spherocytosis (HS) is the most common congenital hemolytic anemia in Europe and North America, with a frequency of 1:2000. It is characterized by erythrocyte membrane fragility due to mutations in erythrocyte membrane proteins, including ankyrin, alpha and beta spectrin, band 3 and protein 4.2 [1]. Clinical signs are highly variable. HS may be asymptomatic or may induce recurrent hemolytic anemia with jaundice, splenomegaly and asthenia. When regular blood transfusions are no longer sufficient to manage severe symptoms, splenectomy may be required. Total splenectomy (TS) has been the gold standard surgery approach for years. However, TS is associated with an increased risk of infection, overwhelming post-splenectomy sepsis (OPSS) in its most severe form, venous thrombosis, atherosclerosis and pulmonary hypertension [2–4].

These potential complications have led to an increasing interest in partial splenectomy (PS). PS was first proposed by Tchernia et al., in 1993 [5], particularly for children younger than 5 years of age. The aim was to remove enough spleen (80 %) in the hope to efficiently prevent hemolysis and reduce the OPSS risk due to the presence of residual spleen parenchyma [6,7]. Nevertheless, PS has several drawbacks. First, surgery may be more complex than for TS with a risk of **intraoperative** bleeding. More importantly, PS long-term efficacy is a matter of concern due to the possibility of residual spleen growth, and consequently of hemolysis recurrence that will require blood transfusions or completion splenectomy.

PS efficacy has been a subject of debate. Previous studies suggest that PS may probably be less effective than TS with a lower increase of hemoglobin concentration after surgery [8–10]. Unfortunately, these studies did not determine predictors of lower efficacy [11] and most often provided only short-term results. The paucity of long-term data is a matter of concern because a meta-analysis suggests a decrease in PS efficacy over time and hemoglobin concentration reduction at 5–6 years post-surgery [12].

Therefore, the aim of this French nationwide retrospective study was to compare the long-term efficacy of TP and PS in children with HS.

2. Materials and methods

This French national multicenter retrospective study included all pediatric patients (younger than 18 years at surgery) who underwent TS or PS for HS in 11 pediatric surgery centers between January 2005 and December 2017. The minimum post-surgery follow-up for inclusion was 5 years. Children who had splenectomy after a trauma or for another reason than HS were excluded.

At each center, the choice between PS and TS was based on the center practice and was not decided based on laboratory parameters. In PS, at least 75 % of the spleen was resected. **OPSS was defined as a rapidly progressing, life-threatening infection that occurs in individuals who have undergone splenectomy (removal of the spleen) or have hyposplenism (reduced spleen function) caused by encapsulated bacteria. The clinical course may rapidly progress to coma and death within 24 to 48 h** [13].

The main primary endpoint was the hemoglobin concentration at the end of the post-surgery follow-up without transfusion. Other data included the initial indication for splenectomy, **intraoperative** and post-operative complications, length of hospital stay at splenectomy time, number and severity of infectious events (including OPSS), occurrence of thrombotic events, use of antibiotic prophylaxis and vaccines, **persistence of asthenia after surgery (from clinical records and parents' reports, and defined as tiredness with repercussions on the child's schooling and physical activity),** and necessity of additional surgery (completion splenectomy after PS).

2.1. Statistical analysis

The statistical analysis was performed by the department of statistics. Patients' characteristics were presented using mean and range for continuous variables, numbers and frequencies for categorical variables. Groups (PS and TS) were compared with the Fisher's exact test for categorical variables and the Mann–Whitney test for continuous variables because data were not normally distributed. Odds ratios (ORs) were calculated with their 95 % confidence intervals (CIs). Results are expressed as median and/or mean values. Event-free survival was compared between groups using Kaplan–Meier curves. **A multivariate analysis was also performed to compare patients who required completion surgery and those who did not.** Statistical analyses were performed with SAS Enterprise Guide 8.2 by the Medical Information Department. For all tests, a significance level (alpha) of 0.05 was used.

As this was a retrospective study, it was validated ethically and regulatory by the coordinating center (Montpellier), and this was considered sufficient by the participating centers under a centralized agreement framework (IRB-MTP_2021_12_202100988, obtained on 16/12/2021).

3. Results

3.1. Overall descriptive analysis

Overall, 96 children who underwent splenectomy for HS were included. The mean age at splenectomy was 7.8 years (± 3.74, median: 7 years), and the mean post-surgery follow-up was 8 years (5 to 17 years, median: 7 years). The majority were boys (n = 63; 65 %). **The indications for splenectomy were: asthenia despite optimal medical treatment (56 %, n = 54), repeated transfusions (38 %, n = 39.5),** laboratory criteria of hypersplenism (14.5 %, n = 14), or major splenomegaly (10.4 %, n = 10). Seventy patients (72.9 %) underwent TS and 26 (27.1 %) PS. **Children in the TS group were older than those in the PS** group (**8.8 years vs 5.35 years, p < 0.01**). **Overall, most surgical procedures were performed laparoscopically (72.9 %, n = 70; 6 for PS and 64 for TS, p < 0.01**), and the mean hospital stay was 5 days (2–19 days). Hemoglobin concentration was 8.99 g/dl (±1.41) before surgery and it rose to 13.54 g/dl (±1.83) after surgery. No post-surgery thrombotic event was reported.

3.2. Comparison between TS and PS

Comparison of efficacy: Clinically, asthenia persisted in seven patients after PS and in none after TS (27 % vs 0 %, p < 0.001). At the post-surgery follow-up end, biologically, hemoglobin concentration was significantly higher in the TS than PS group (13.86 g/dl ± 1.74 vs 11.87 g/dl ± 1.28, p < 0.01) (Table 1). Similarly, the hemoglobin increase was higher in the **TS than PS group (+53.7 % vs +29.8 %, p < 0.01). A multivariate analysis, to control for several confounding factors (age at surgery time, symptoms that led to the splenectomy decision, preoperative hemoglobin level, or surgical technique), confirmed the higher efficacy of TS.**

Post-operative course: The rate of early postoperative complications was not significantly different between the PS and TS groups (15.4 % vs. 11.4 %, p = 0.89) (Table 1). Particularly, the risk of bleeding events and the necessity of transfusion during surgery were not higher in the PS than TS group (4.3 % vs 3.8 %, p > 0.05). Conversely, hospital stay duration was statistically longer in the PS than TS group (6.9 ± 2.6 days vs 4.9 ± 2.5 days, p < 0.01).

Rate of post-operative infections: Overall, only four children had an infection (4.2 %; n = 2 ear, nose, throat infections; n = 1 cellulitis; n = 1 not specified), but none OPSS. All infections occurred in children older than 5 years of age (Table 1). The infection rate was not significantly different between the TS and PS groups (n = 3; 4.2 % vs. n = 1; 3.8 %, p = 0.93). However, post-surgery antibiotic prophylaxis was longer in the TS than PS group (5.34 ± 2.82 years vs 4.10 ± 4.27 years, p = 0.03). Immunization coverage was similar between groups: high against *Streptococcus pneumoniae* and low for *Neisseria meningitidis* and *Haemophilus influenzae* (Table 1).

3.3. Completion splenectomy after PS

C**ompletion** splenectomy was required in 11/26 children (42.3 %) due to recurrent red blood cell sequestration, leading to persistent anemia and regular transfusions. In one patient, rescue TS was performed early due to a delayed hemorrhage after PS. **In the 11 patients who required completion splenectomy, the mean pre-PS hemoglobin concentration was 7.9 g/dl (range 6.3 g/dl to 9 g/dl), the mean interval between PS and completion surgery was 7 years (median 6.1 years, range: 2 days to 22 years), and their mean age at completion splenectomy was 11.5 years (median 11.9 years). Before completion splenectomy, the mean hemoglobin concentration was 9.75 g/dl (range: 9 g/dl to 10.5 g/dl). Splenectomy completion was performed by open surgery in 7/11 patients (63.6 %). Late completion splenectomy was not uncommon in our series: 25 % of such surgeries was performed more than 8 years after PS, and in one case after 17 years (event-free survival curve in Fig. 1). In the completion subgroup, the rate of intra-operative complications was high (n = 2, 18 %; n = 1 diaphragmatic injury with immediate repair and n = 1 surgical site infection). Completion splenectomy was effective because hemoglobin concentration increased from 11.8 g/dl ± 1.28 after PS to 14.49 g/dl ± 1.34 after completion surgery (p < 0.01), a level similar to that in the TS group at the post-surgery follow-up end (13.86 g/dl ± 1.74, p = 0.15).** The only difference between patients who required **completion splenectomy** and those who did not was the baseline hemoglobin concentration before PS (7.9 g/dL vs 9 g/dL, p < 0.01) in both univariate and multivariate analyses. Hemoglobin concentration <8.5 g/dL significantly increased the risk of **completion** splenectomy in our series (OR = 10; 95 %; CI [2.23–100]; p = 0.03).

4. Discussion

PS has been proposed for HS as an alternative to TS to reduce the risk of infections [5]. However, its efficiency may decrease over time, leading to the need of transfusions and sometimes, **completion splenectomy** [8,9,14,15]. Therefore, the aim of this study was to compare the long-term efficacy of PS and TS in order to clarify the need of long-term follow-up after PS and to identify patients at risk of **completion splenectomy**.

We found that in our series, after a mean follow-up of 8 years, PS was less effective than TS based on laboratory (hemoglobin concentration) and clinical data (asthenia). Specifically, hemoglobin concentration at the post-surgery follow-up end was significantly lower in the PS than TS group (p < 0.01). Moreover, during the post-surgery follow-up, patients in the PS group reported recurrent asthenia and repeated transfusions, leading to completion splenectomy in 42 % of patients. This result may appear to be in contradiction with previous studies that showed no difference in hemoglobin concentration after PS and TS and low **completion splenectomy rates** (24 **%). However, their**

Table 1
Comparison of clinical characteristics in the total splenectomy (TS) and partial splenectomy (PS) groups.

	TS n = 70	PS n = 26	p
Sex (number)			
Females	47	10	<0.03
Males	23	16	
Mean hemoglobin concentration before surgery (g/dL)	9.1 (±1.5)	8.5 (±0.9)	>0.05
Mean hemoglobin concentration at the post-surgery follow-up end (g/dL)	13.9 (±1.7)	11.9 (±1.3)	<0.01
Mean hospital stay duration (days)	5.3 (±2.9)	6.1 (±1.5)	<0.03
Mean age at surgery (years)	8.8 (3–15.5)	5.3 (1–10.5)	<0.01
Surgery techniques (number)			
Open surgery	6	20	<0.01
Laparoscopic surgery	64	6	
Completion splenectomy (number)	NA	11 (42.3 %)	NA
Post-surgery complications (percentage)	8 (11.4 %)	4 (15.4 %)	0,89
Number of infectious events after surgery (percentage)	3 (4 %)	1 (3.8 %)	0.93
Antibiotic prophylaxis duration (years)	5.3 (±2.9)	4.1 (±4.8)	0.03
Vaccination rate for			
Haemophilus influenzae	41 (58 %)	11 (42 %)	ns
Meningococcus A, C, Y, W135	31 (44 %)	12 (47 %)	ns
Meningococcus B	39 (55 %)	14 (54 %)	ns
Meningococcus C	34 (49 %)	16 (61 %)	ns
Streptococcus pneumoniae	68 (97 %)	23 (88 %)	ns

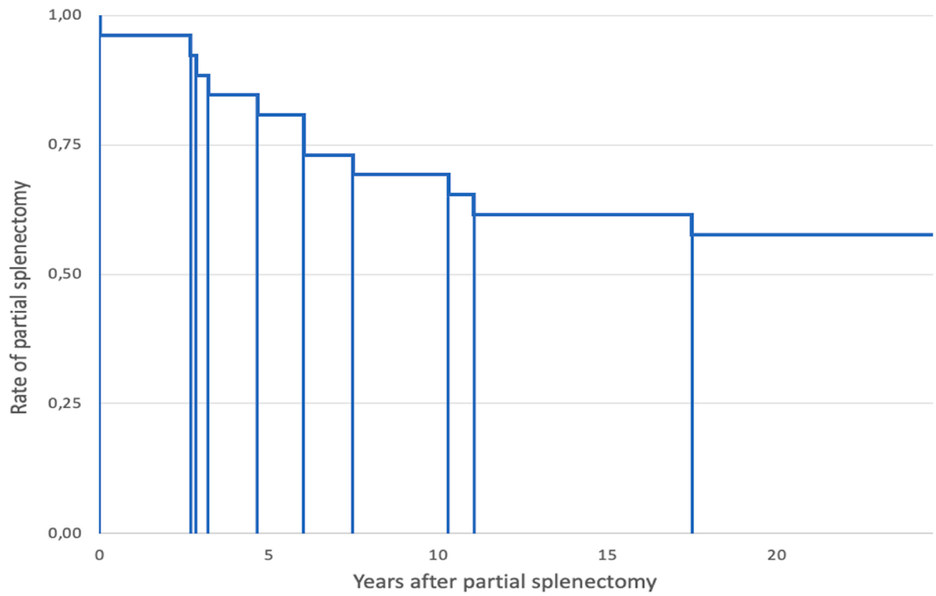

Fig. 1. Kaplan-Meyer event-free survival curve (event = completion splenectomy) of patients who underwent partial splenectomy (n = 26).

follow-up periods were relatively short (2–3 years) [11][12] and this might have led to underestimating the slow decline in hemoglobin concentration that can occur during late infancy and adolescence [8]. A previous study demonstrated that PS efficacy tends to decrease over time, despite the initial increase in hemoglobin concentration (+2.2 g/dL at 1 year; +3.2 g/dL at 3–4 years; +2.2 g/dL at 6 years post-surgery) [12]**. This trend is clearly reflected in our series where 25 % of completion splenectomies were carried out more than 8 years after the initial PS (17 years for one patient)**. The event (completion splenectomy)-free survival curve did not show a time from when the need of **completion** splenectomy stabilizes and stops. This is clinically relevant to improve parental counselling, to reduce the number of patients lost to follow-up, and to improve care during adolescence even when the hemoglobin concentration is stabilized in the first years after PS.

The next step is to identify which patients are most likely to benefit from PS. Hafezi et al. **reported that none of the preoperative parameters analyzed (hemoglobin concentration, hematocrit, reticulocyte count, total bilirubin, spleen size) could predict the need of completion splenectomy** [11]. **Conversely, our analysis suggests that patients with a preoperative hemoglobin concentration <8.5 g/dL are particularly at risk of requiring completion splenectomy, similarly to what reported in a previous study** [15]. **Indeed, a low pre-surgery hemoglobin concentration is indicative of more pronounced splenic hemolysis. In agreement, Rosman** et al. **proposed that higher preoperative disease severity correlates with an increased likelihood of completion splenectomy** [16]. In these patients, the post-PS residual spleen volume may be enough to maintain a significant level of hemolysis that increases the risk of additional surgery. Therefore, patients with low pre-surgery hemoglobin concentration will require close monitoring throughout adolescence if PS is carried out.

Besides the difference in efficacy, the risk of intra- and post-surgery complications was not different in the TS and PS groups**, although previous studies suggested that this risk is higher for PS** [15]**. Unlike what reported by a meta-analysis** [12]**, the length of hospital stay was shorter in the TS group, but this may be due the extensive use of laparoscopy in this group. The high rate of open procedures compared with laparoscopic approaches in our series could be explained by the priority given by many centers to successfully perform a PS.** We did not identify an increased risk of OPSS after TS, compared with PS, but our study was not designed to address this point. Indeed, this would require a larger sample to increase the statistical power due to OPSS rarity (0–5 %) [2,3] and also a standardized protocol for infection prevention to be used in both groups. In the present work, the longer antibiotic prophylaxis and the higher immunization rate in the TS group may have contributed to the low infection rate, thus preventing us from drawing any definitive conclusion on this point. Therefore, this observation should not be used to question the potential benefit of PS especially in young children. More studies to quantify the reduction in infection risk after PS are needed to put our observation into perspective.

The strong points of our study are the length of follow-up, the multicenter design and the sample homogeneity (only pediatric patients with HS). However, several limitations should be noted. First, each center had its own indications for PS/TS and **completion** splenectomy, according to local practice. **As a result, potential confounding factors, such as patient age at surgery and surgical approach, might have introduced some bias in the patient selection. The gradual decrease in hemoglobin concentration and the potential need for completion splenectomy are not affected by these confounding factors. A randomized controlled study is needed to avoid these bias.** Second, the patient follow-up was not standardized and we used the hemoglobin concentration at the follow-up end as the outcome without considering the hemoglobin concentration kinetics throughout the years after surgery. Third, as the spleen volume after PS was not quantified, the volume removed by the surgeon remained subjective. This could have affected the residual spleen functionality and consequently PS efficacy. **Fourth, asthenia could have been quantified with standardized and validated questionnaires used in other pediatric pathologies (PedsQL or QFES)** [17]. **Fifth, the data on the absence of severe infectious episodes (OPSS) are reassuring. However, the limited statistical power of our sample and the possible protective effect of the extended antibiotic prophylaxis in the TS**

group warrant continued caution. Last, our findings are valid only for HS, and specific studies are necessary for other conditions, such as sickle cell disease.

To conclude, in children with HS, hemoglobin concentration is lower after PS than after TS and patients who undergo PS may require splenectomy **completion even many years after the initial surgery**. **Therefore, after PS, long-term monitoring of hemoglobin concentration is required**, particularly in patients with a pre-surgery hemoglobin concentration <8.5 g/dl. On the other hand, **PS efficacy in reducing infectious complications must be demonstrated in a large comparative cohort study.**

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