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Splenic autotransplantation: A systematic review

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Abstract

Background: Splenectomy is a surgical procedure indicated in a variety of medical conditions including trauma. Postoperatively, there is a lifelong risk of developing overwhelming sepsis from encapsulated bacteria, most commonly due to *Streptococcus pneumoniae*. Splenic autotransplantation has been proposed as a method to recover splenic function in patients requiring splenectomy with otherwise normal spleens. This paper aims to systematically review the literature to determine the efficacy of spleen autotransplantation.

Methods: MEDLINE, PubMed and the Cochrane Library were searched for all studies assessing splenic autotransplantation (January 1947 to July 2018). Data was extracted on study characteristics, outcomes assessed, including spleen scintigraphy results, blood film counts and serum immunoglobulin levels.

Results: Data was obtained from 18 primary studies. All papers demonstrated return of regenerated spleen tissue in the majority of their patients (95.3%) on spleen scintigraphy. 90.2% of patients in 12 studies had blood films return to normal following transplantation. Immunoglobulin levels were shown to return to normal in all 12 studies where it was assessed. 3.7% of patients in 11 studies had postoperative complications. 1.3% of patients in five studies had postoperative infections in the follow-up period.

Conclusion: Splenic autotransplantation is a safe procedure with minimal complications that can return splenic filtration function and immunoglobulin levels to normal ranges. It has not been confirmed whether autotransplantation provides meaningful protection against overwhelming postsplenectomy infections.

Keywords: splenic autotransplantation, spleen, splenectomy

Introduction

The protective role of the spleen against infection has been established since the 1950s when severe sepsis and death were described in splenectomy patients[1]. As such the role of splenectomy, especially in trauma, has been re-evaluated. Although preservation is recommended in over 90% of splenic trauma, splenectomy is still an indicated procedure for haematological, malignant and non-malignant causes[2,3].

The major risk to splenectomised patients is overwhelming postsplenectomy infection (OPSI). These patients can develop fulminating sepsis, meningitis or pneumonia as they are no longer able to filter encapsulated bacteria such as *Streptococcus pneumoniae*[4,5]. There remains some uncertainty in the existence of OPSI, especially in adults, as the incidence is low. However numerous retrospective studies have documented severe infections in splenectomised patients [5,6]. The rate of infection has been estimated at 3.2% with a mortality rate of 1.4%[6]. Of those patients with OPSI, up to 68% die within the first 24 hours[5]. The risk of OPSI is lifelong and has been described even 20-40 years postsplenectomy[7,8].

The current Australian recommendations suggest that in addition to vaccinations and enrolment onto the spleen registry, patients receive prophylactic antibiotics for at least three years in otherwise healthy patients, and lifelong in those who are immunocompromised[9,10]. However, the use of antibiotics for prevention of OPSI is not

evidence based[4]. There is minimal data on their actual effectiveness, and no consensus on the duration of preventative antibiotics[11].

One potential way to recover splenic function postsplenectomy is by splenic autotransplantation, that is, the reimplantation of splenic material back into the abdominal cavity. If return of effective splenic function can be achieved, this procedure may be able to reduce a patient's risk of OPSI, as well as other potential risks including thrombosis[12]. This idea is based on the phenomenon of splenosis, the autotransplantation of splenic tissue from ruptured spleen into the peritoneal cavity. Dubbed the 'born again' spleen, it was observed that up to 50% of patients who received a splenectomy for trauma had substantial amounts of ectopic spleen tissue, and it was hypothesised that this may account for the relative low incidence of OPSI in this population[13].

Return of splenic function has been investigated in several ways in the literature. This can be divided into determining the return of filtrating function and immunological function.

Howell-Jolly bodies (i.e. erythrocytes with nuclear remnants), and pitted red cells are both filtered out by the spleen and have been evaluated as markers of splenic filtration function[14].

Spleen scintigraphy uses technetium 99m labelled, heat altered autologous erythrocytes or sulphur colloid, which are then largely sequestered by the spleen[4,14]. When combined with computed tomography (CT), both function and volume of reimplanted spleen can be determined in a single investigation[14,15].

Immunological function has been measured through titres of immunoglobulins such as IgM, IgG and complement levels in the literature. Decreased levels of IgM have been described in patients with diminished splenic function, but return of normal levels of IgM after splenic autotransplantation have not been validated to show whether they indicate protection against infection[4,14].

Recently, there has been increased interest in the use of splenic autotransplantation in elective procedures, where spleen mass and quality can be preserved. However, there is no consensus on how surgeons should attempt to reimplant this tissue or whether this provides any return of function, especially protection against pneumococcal infection.

This systematic review aims to assess the literature for all outcomes assessing the return of splenic function after autotransplantation and to consolidate current methodology regarding autotransplantation of spleen tissue.

Methods

We conducted a systematic review of studies assessing splenic function post spleen autotransplantation. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines[16].

Search strategy and study selection

We searched MEDLINE, PubMed and Cochrane libraries for articles published between 1 January 1947 and 31 July 2018. The search terms consisted of [['spleen' or 'splenic'] AND ['autotransplantation' or 'autotransplant' or 'transplantation' or 'transplant' or 'reimplantation' or 'reimplant' or 'replant' or 'replantation' or 'implant' or 'implantation']]. The reference lists of eligible articles were searched for other relevant publications to identify additional studies.

Titles or abstracts for all studies were identified by the initial search from the reviewer (AS) and irrelevant studies were excluded. For the remaining studies, full-text articles were retrieved and evaluated to determine whether they met the inclusion criteria.

We included English-language studies on human subjects assessing splenic function in any way after spleen autotransplantation. Studies assessing splenosis were excluded.

All outcomes in the remaining studies were collected. We included all randomised and non-randomised comparative studies, single cohort studies and case series. Case reports, narrative reviews, editorials, conference abstracts, and publications in languages other than English were excluded.

Data extraction and quality assessment

Data were independently extracted by one reviewer (AS) onto a data extraction sheet, which included publication year, sample size, study design, country of study, type of patients, patient characteristics, indication for implantation, size of implant, method of implantation, outcomes, complications, postoperative infections and conclusions.

Synthesis

We planned to perform statistical meta-analysis only if studies had sufficiently similar cohorts and outcome measures. Otherwise we planned to perform narrative analysis of the results, presenting them in tabular form.

Results

Search strategy and selection

The search strategy yielded 676 citations, 25 of which were potentially relevant and were reviewed in full text (Figure 1). Six studies did not meet inclusion criteria and were excluded[17–22]. Two studies used the same patient cohort, and the earlier study with fewer data points was excluded[23]. This left a total of 18 primary studies[24-41]. Reviewing reference lists from these studies identified no other eligible articles.

Characteristics of included studies

The study characteristics of the primary studies are summarised in Table 1. The included primary studies were published between 1981 and 2012.

All 18 primary studies were single centre. Six of these studies compared outcomes from a spleen autotransplant cohort to a splenectomised cohort[31,33,36,38-40].

The main indication for splenic autotransplantation was trauma[24-28,30-36,39,41]. Patients with portal hypertension[37,38,40] and chronic pancreatitis[29] were also indications for autotransplantation in the assessed studies, as well as patients undergoing a vagotomy[28] or a partial gastrectomy[36].

Implanting splenic tissue into the greater omentum was the method used in 16 studies. The remaining two studies implanted splenic tissue into the retroperitoneum[38] and into an extraperitoneal pouch[30].

All studies had varying methods in terms of the amount of splenic tissue reimplanted and how it was prepared. Three studies[33-35] used a technique for spleen autotransplantation developed by Seufert et al.[42], however, this was not further elaborated on by any of the studies. Two studies had no information on the amount of spleen reimplanted[34,35]. Of the remaining 16 studies, 14 used at least 20g of spleen tissue[24,27-33,36-41].

Outcomes in primary studies

Table 2 qualitatively summarises the outcomes in all primary studies.

Scintigraphy

Spleen scintigraphy was used in all studies assessing return of splenic function. Scans were performed at least two months post implantation. Positive spleen scans were evaluated as those having intact and functional splenic tissue in the transplanted areas, however quantifiable analysis of the amount of viable spleen was only assessed in one

study which corresponded larger implantation volumes with fewer immunological alterations[35]. 95.3% (201/211) of patients had positive spleen scintigraphy.

Blood film (HJ bodies/pitted red cells)

Assessments of blood films were done in 12 studies. Nine studies assessed Howell-Jolly bodies post splenic autotransplantation, two measured the number of pitted red cells and one commented on blood film generally. Of the 11 studies providing quantitative results, 90.2% of patients (110/122) had blood films returning to pre-operative states, with either the absence of Howell-Jolly bodies or normal levels of pitted red cells. One study commented generally on patients' blood films, stating that these returned close to pre-operative levels[29].

Immunoglobulins (IgM)

Immunoglobulin levels, specifically IgM, were assessed in 12 studies. These levels returned to the normal range in all cases. Of the six comparative studies, three found IgM levels in the normal range for the autotransplantation cohort, compared to the splenectomised cohort which was below normal limits[38-40].The other three studies found levels in the normal range for both the autotransplantation and the splenectomised cohorts[31,33,36].

Complications

Complications related to the autotransplantation procedure was reported in 11 studies. The overall complication rate was 3.7% (5/138). Of these, four were described as postoperative ileus[31,32], and one other as a subphrenic abscess[28]. One patient required a division of adhesions[31], while the rest of these complications were managed conservatively. No intraoperative complications were described.

Postoperative infections

Five studies commented on whether patients developed any infections during their respective follow-up period[31,32,35,36,40]. Only one case of pneumonia was reported which was managed with antibiotics[35]. The overall postoperative infection rate in these studies was 1.3% (1/75).

Discussion

Based on the available evidence, we conclude that splenic autotransplantation can return spleen filtration function and return immunoglobulin levels to normal ranges. Whether normal IgM levels results in return of immunological function is unclear. It was also found to be a safe procedure with minimal complications both intraoperatively and postoperatively.

This review highlights the large discrepancy in the transplantation techniques described in the literature. The amount and preparation of harvested splenic tissue as well as the location of spleen implantation has not been standardised. Many of the studies assessed used the omentum to secure splenic tissue with success, compared to implanting into the retroperitoneum which resulted in poorer scintigraphy results[30], or into an extraperitoneal pouch, which had higher pitted red cell counts[38]. These results correlate with animal trials which show greater transplant uptake in the omentum compared to the peritoneum or rectus muscle[43–45]. The precise reason why spleen autotransplantation regenerates better in the omentum is unknown, though it has been hypothesised that this may be due to its rich vascular supply allowing for neovascularisation and its drainage into the portal venous system, which matches the spleen's own blood flow[21,27,28,46].

There is also no consensus on how spleen tissue harvested for transplantation is to be prepared. Spleen slices seem to be the preferred technique[24-26,30-32,37,40,41], though mincing spleen tissue has also been used in the literature with no apparent discernible effect on outcome.

The critical mass of perfused splenic tissue has not been standardised in the literature. The initial study assessing splenosis by Corazza et al.[18] estimated at least 30cm^3 of functional tissue was required to provide return of spleen function, based on scintigraphy volumes. Since then, only one of the included studies estimated volumes of functional spleen post autotransplantation, stating only that larger implantation volumes had fewer immunological alterations[27]. Animal studies suggest reimplantation of 25-50% of spleen volume to provide improved phagocytic function and pneumococcal protection[43,44]. Higher volumes may also be needed due to the initial necrosis of the implants while they establish neovascularisation which may reduce the total functional spleen[26,47]. Based on the evaluated studies, using a minimum of 20cm^3 of prepared spleen, implanted into the greater omentum, would likely provide positive results, however these recommendations are unproven and any future studies should assess functional volumes postoperatively to determine the critical mass of remaining spleen once it has vascularised.

All evaluated studies report the return of a normal blood film and positive scintigraphy results after splenic autotransplantation, suggestive of active spleen filtration function.

Immunological function, however, is more difficult to assess. Although IgM levels did return to within normal limits post autotransplantation in the reviewed studies, its use as a true indicator for splenic immunological function and protection against infection is yet to be confirmed[14,22].

The ultimate test of splenic function is a pneumococcal challenge though this is not feasible in human studies[22]. While animal studies have shown promising results with higher infection clearance rates and survival in autotransplanted rats compared to splenectomised cohorts[43,44], there have been case reports of humans with splenosis and even splenic implants developing OPSI[48,49]. A review by Holdsworth et al.[21] found 14 cases of this, suggesting that even large amounts of regenerated spleen may not provide any benefit. Quantity, quality and location of regenerated spleen in these cases may be of relevance, and it has been hypothesized that the high rate of splenosis that does occur in trauma, may explain the low incidence of OPSI in this cohort[21].

New investigations, such as IgM memory B cells, which may play a more specific role in antibody response, and tuftsin, a peptide regulating phagocytic cells, have also been shown to correspond with states of asplenia and may provide further information about return of splenic immune function[14,50]. But until these tests have been validated, vaccinations and antibiotics should be recommended practice for all splenectomised patients.

Splenic autotransplantation appears to be a safe and simple procedure with minimal postoperative complications. It is unclear however, whether the documented complications are directly related to the splenic implant or if they could be classified as general surgical complications. Furthermore, all complications occurred in studies transplanting trauma patients, which may have a higher incidence of complications due to injury mechanism and potential wound contamination. Necrosis of implants with subsequent abscess formation has also been documented in the literature, likely due to their initial lack of blood supply[20,51].

Although immune function and subsequent protection against OPSI is the major outcome of assessing splenic autotransplantation, the documentation of infections in the literature has been poor. Only five studies evaluated their cohort for infection or OPSI in their follow up period, despite all studies mentioning the significance of OPSI within their discussion. This may be due to the short follow up periods in these studies, the use of vaccinations and prophylactic antibiotics, or due to the low incidence of OPSI[6]. Future studies will need to ensure that OPSI infections are monitored long-term, to supplement biochemical parameters in assessing return of splenic immunological function.

The role in which splenic autotransplantation is indicated has expanded from its original purpose. Traumatic splenic injuries, which were once the initial indication for attempting splenic autotransplantation, has now changed in light of non-operative management and spleen preservation techniques[2,3]. The shift in transplantation is now seen in

elective splenectomies for unrelated conditions where spleen quality can be preserved. This procedure may also be considered in patients undergoing distal pancreatectomy, where it may be difficult, or in fact not appropriate, to preserve splenic vessels due to their intimate nature with the pancreas. Regardless of the indication, the procedure itself is a simple technique that specialist hepato-pancreato-biliary and upper gastrointestinal surgeons as well as trauma surgeons can easily perform[21,22].

The reason for performing splenic autotransplantation however, has not changed since its inception almost 40 years ago. OPSI is still a major risk for splenectomised patients which remains lifelong[7,8]. Despite this, little progress has been made on determining whether this procedure provides any utility in preventing these infections and has prevented it from being adopted as standard practice in this cohort of patients.

Conclusion

Splenic autotransplantation is a safe procedure that can return spleen filtration function and return immunoglobulin levels to normal ranges, however, it is still uncertain as to whether it provides any protection against OPSI. This systematic review highlights the lack of clear protocol regarding the procedure, as well as the difficulty in evaluating return of immune function in these patients. As postsplenectomy sepsis is an uncommon occurrence, a large-scale trial with a long period of follow-up would be

recommended to assess whether a protective effect of autotransplantation against infection exists. The results of such a study could have a widespread impact on the management of patients requiring emergency or elective splenectomies.

Conflicts of interest

None declared.

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Tables

Table 1: Primary study characteristics

Primary Studies	Year	Country	Study Design	Indication	No. of patients (other cohorts)	Technique
Patel et al. [24]	1981	USA	Retrospective	Trauma	4	2 slices of spleen, 3mm thick, 20g total, into greater omentum
Velcek et al. [25]	1982	USA	Retrospective	Trauma	3	15-20 slices, 15x15x2mm, 6-9g total, into greater omentum
Millikan et al. [26]	1982	USA	Retrospective	Trauma	23	5 slices, 20x20x5mm, 10g total, into greater omentum
Durig et al. [27]	1984	Germany	Retrospective	Trauma	9	Homogenised spleen, 50-100g total, into greater omentum
Nielsen et al. [28]	1984	Sweden	Retrospective	Trauma and vagotomy	14	Homogenised spleen, 50g total, into greater omentum
Nicholson et al. [29]	1986	UK	Retrospective	Chronic pancreatitis	6	2-3mm cubes, 30-50g total, into greater omentum
Traub et al. [30]	1987	USA	Prospective	Trauma	7	Thinly sliced spleen, 25-30g total, into extraperitoneal pouch
Buyukunal et al. [31]	1987	Turkey	Retrospective	Trauma	16 (splenectomy n=10)	2-4 slices, 30x50x5mm, 15g-30g total, into greater omentum
Mizrahi et al. [32]	1989	Israel	Prospective	Trauma	10	3mm thick slices, 50g total, into greater omentum
Ludtke et al. [33]	1990	West	Retrospective	Trauma	20	Seufert method,

		Germany			(splenectomy and splenosis n=14; splenectomy, no splenosis n=7)	20-40g, into greater omentum
Budihna et al. [34]	1991	Yugoslavia	Prospective	Trauma	13	Modified Seufert method, No information provided into greater omentum
Weber et al. [35]	1998	Germany	Retrospective	Trauma	8	Seufert method, No information provided into greater omentum
Leemans et al. [36]	1999, 1996	Netherlands	Prospective	Trauma and partial gastrectomy	10 (splenectomy n=14)	2-3mm cubes, 25g total, into greater omentum
Brandt et al. [37]	2001	Brazil	Retrospective	Portal HTN secondary to schistosomiasis	23	10 slices, 3x2x2 cm, 100g total, into greater omentum
Zhang et al. [38]	2002	China	Prospective	Portal HTN and liver cirrhosis	10 (splenectomy n=10)	7x5x1 cm fragment, 35g total, into retroperitoneum above left kidney
Resende et al. [39]	2002	Brazil	Prospective	Trauma	20 (splenectomy n=9; control n=22)	1x1x1cm cube, 22 fragments, 22g total (estimated), into greater omentum
Petroianu et al. [40]	2005	Brazil	Prospective	Portal HTN secondary to schistosomiasis	31 (trauma splenectomy and partial splenectomy n=36)	20 spleen slices 1-2cm thickness, 50g total, into greater omentum
Di Carlo et al. [41]	2012	Italy	Prospective	Trauma	4	4x3x2cm slice, 35g total, into greater omentum

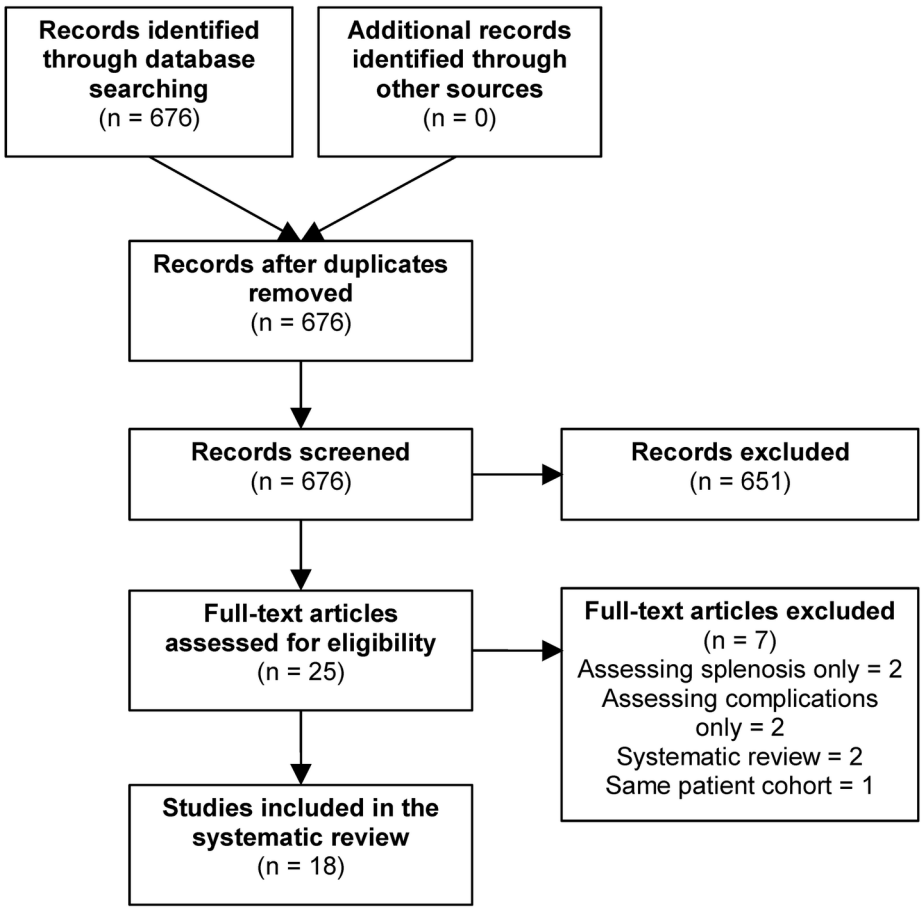
HTN, hypertension

Table 2: Study outcomes

Primary Studies	Positive spleen scintigraphy	Normal blood film	IgM	Complications	Post-operative infections
Patel et al. [24]	4/4	4/4 †	Normal range	0	-
Velcek et al. [25]	3/3	3/3 †	Normal range	-	-
Millikan et al. [26]	12/12	-	Normal range	0	-
Durig et al. [27]	9/9	-	-	-	-
Nielsen et al. [28]	6/6	6/6 ‡	Normal range	1	-
Nicholson et al. [29]	4/6	5/6 §	-	-	-
Traub et al. [30]	7/7	1/7 ‡	-	0	-
Buyukunal et al. [31]	16/16	No figures †	Normal range	2	0
Mizrahi et al. [32]	10/10	10/10 †	Normal range	2	0
Ludtke et al. [33]	20/20	-	Normal range	-	-
Budihna et al. [34]	13/13	5/8 †	-	0	-
Weber et al. [35]	7/8	-	Normal range	-	1
Leemans et al. [36]	10/10	-	Normal range	0	0
Brandt et al. [37]	21/23	21/23 †	-	-	-
Zhang et al. [38]	4/9	-	Normal range	0	-
Resende et al. [39]	20/20	20/20 †	Normal range	0	-
Petroianu et al. [40]	31/31	31/31 †	Normal range	0	0
Di Carlo et al. [41]	4/4	4/4 †	-	-	-

IgM, immunoglobulin M;

† Howell-Jolly Bodies; ‡ Pitted Red Cells; § Blood Film



ANS_15383_Figure 1 - PRISMA flowchart depicting the search strategy and selection of articles for the review.tif