

Efficacy and safety of antegrade sclerotherapy for varicocele in pediatric patients: A systematic review

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Abstract

Objectives: Antegrade sclerotherapy (Tauber's) procedure has been extensively used for the minimally-invasive treatment of varicocele; however, the results in the pediatric population are less defined. This systematic review evaluates the efficacy and safety of antegrade sclerotherapy for varicocele in the pediatric population.

Evidence acquisition: The review was conducted following the PRISMA guidelines. Systematic research of available literature in English language from 1980 until May 2022 was conducted through EMBASE, MEDLINE, Cochrane Library, and NIH Registry of Clinical Trials. For each study, information was gathered regarding the study design, the inclusion/exclusion criteria, the indications for treatment, the success rate and the complications. When available, the details about sperm analysis were reported.

Evidence synthesis: The 10 studies were included in the final sample (564 patients). Median age of patients ranged 13.3–15.3 years. The indications for scleroembolization varied in the different studies, while most studies included patients with clinical G2-G3 varicocele and clinical symptoms or testicular asymmetry. The treatment was successful in 88%–98% of the patients, while the complication rate was <5%.

Conclusion: Tauber's sclerotherapy is a safe and effective treatment for varicocele also in the pediatric population. Further studies with standardized inclusion criteria are needed to provide higher level of evidence and compare the outcomes of antegrade sclerotherapy with the other available techniques.

Keywords

Varicocele, pediatric, Tauber procedure, antegrade sclerotherapy, scleroembolization

Introduction

Varicocele is an abnormal dilation of testicular veins caused by venous reflux and it is unusual in boys under 10 years of age, while it becomes more frequent at the beginning of puberty. Fertility problems will arise in about 20% of patients with varicocele, since it can induce apoptotic pathways because of heat stress and accumulation of toxic materials. According to EAU guidelines, the recommended indication criteria for varicocelectomy in children and adolescents are: varicocele associated with hypotrophic testis (>20% or >2 cc difference compared to the contralateral), additional testicular condition affecting fertility, bilateral palpable varicocele, pathological sperm quality (in older adolescents), and symptomatic varicocele.¹

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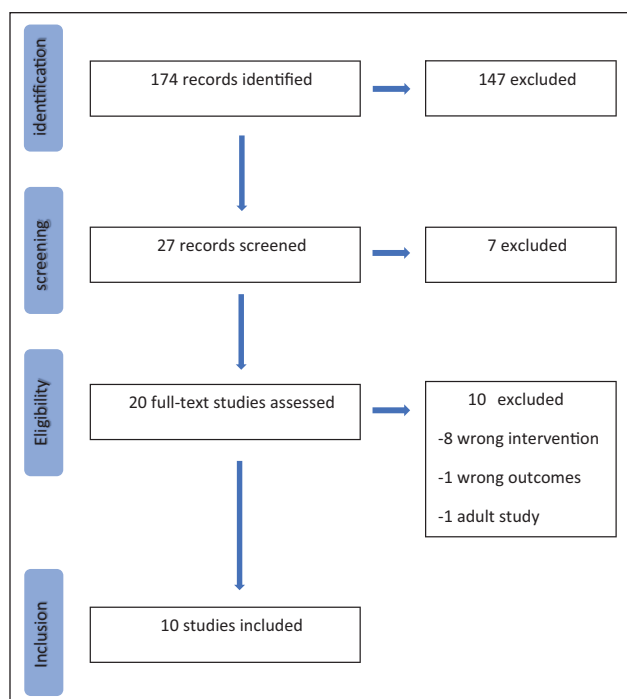


Figure 1. Flow diagram of the study.

Surgical intervention is based on occlusion (antegrade or retrograde sclerotization) or ligation of the internal spermatic veins. Antegrade sclerotherapy (Tauber's) procedure has been extensively used for the minimally invasive treatment of varicocele; however, the results in the pediatric population are less defined. This systematic review aims to evaluate the efficacy and safety of antegrade sclerotherapy for varicocele in the pediatric population, testing the hypothesis that this technique could be effectively performed with low complication rate in the pediatric setting.

Evidence acquisition

The review was conducted following the PRISMA guidelines. Systematic research of available literature in the English language from 1980 until May 2022 was conducted through EMBASE, MEDLINE, Cochrane Library and NIH Registry of Clinical Trials. Clinical trials, cohort studies and case control studies and cross-sectional studies were considered. Case reports and case series were excluded because of their inadequacy for an accurate statistical assessment. A comprehensive search of terms (pediatric varicocele, pediatric scleroembolization, pediatric Tauber, pediatric antegrade sclerotherapy, adolescent varicocele) was performed.

Studies including patients <16 year old undergoing antegrade (Tauber's) scleroembolization for varicocele were considered. Two authors (AM and MB) undertook the study selection, screening the titles and abstracts of articles found in the search and discarding those which did not meet the

Table 1. Risk of bias of the included studies.

Author, year	Selection (max 4*)	Comparability (max 1*)	Outcome (max 3*)
Beutner et al. ²	***		***
Fette and Mayr ³	*		*
Ficarra et al. ⁴	***		*
Hung et al. ⁵	***		***
Keene and Cervellione ⁶	***		**
Mazzoni ⁷	***		
Mazzoni et al. ⁸	***		
Mottrie et al. ⁹	*		
Paradiso et al. ¹⁰	***		**
Zaupá et al. ¹¹	**		*+

eligibility criteria, Covidence online tool (<https://www.covidence.org/>) was used for the screening phase. Full text copies of the eligible articles were obtained. The complete selection process is shown in Figure 1. When the study involved different interventions for varicocele, only patients undergoing AS were considered and included in the table.

For each included study, information was gathered regarding the study design, the inclusion/exclusion criteria, the indications for treatment, the success rate (as defined and reported by the study) and the complications. When available, the details about sperm analysis were reported. Risk of bias for was assessed through the Newcastle-Ottawa Scale and summarized in Table 1.

Evidence synthesis

Characteristics of the included studies

Overall, 174 studies were retrieved using the search strategy, after initial screening, exclusion of irrelevant findings and duplicates, 20 studies were eligible for full text evaluation. The final set included 10 studies (564 patients). Characteristics of the included studies are summarized in Table 2. Median age of patients ranged 13.3–15.3 years. The indications for scleroembolization varied in the different studies, most studies included patients with clinical G2-G3 varicocele and clinical symptoms or testicular asymmetry. Four studies^{2,3,9,10} included G1-G3 varicocele; three studies^{3,6,12} included G2-G3 varicocele; three studies^{5,7,8} included only G3 varicocele.

Antegrade sclerotherapy (AS) was performed in all studies under local or general anesthesia following standard Tauber's procedure.¹³ Three studies compared different techniques (mainly antegrade scleroembolization VS Palomo technique—either laparoscopic or open), in this case the results of the Tauber procedure were recorded.

Success definition was considered as reported by the studies, since no “a priori” definition of success was possible. Most studies considered as success “no varicocele” or “no G2-G3 varicocele,” at the follow up visit and/or at

Table 2. Main features and results of the studies.

Study	Design	Patients	Median age (years)	Follow-up (months)	Inclusion criteria	Indications	Success definition	Success rate (%)	Complications	Recurrence (%)	Sperm parameters
Beutner et al. ²	Cohort, retrospective	67	17.2	69 (median)	Varicocele G1-3	Pain, cosmetic, subfertility (8.9%), hypotrophy	No varicocele at doppler US	88.1	3 (4.5%) Epididymo-orchitis	8 (11.9%)	No
Fette and Mayr ³	Cohort, prospective	21	13	23 (median)	Varicocele G2-3	ND	No G2 clinically/no reflux at US	95.2/80.9	3 (14%) slight hydrocele	1 (4.7%) G2 1 (4.7%) G1	No
Ficarra et al. ⁴	Cohort, prospective	45	15	Minimum 6	Varicocele G1-3	Pain, failure of ipsilateral testicular growth, (parents' request)	No US reflux	97.7	None	1 (2.2%)	No
Hung et al. ⁵	Cohort, retrospective	55	14	12	G 2-3 varicocele	Symptoms > 10% difference in volume, G3	No clinical G2- G3 varicocele	91.6	3 (5.5%)	4 (8.4%)	No
Keene and Cervellione ⁶	Cohort, prospective	91	14.8	22 (median)	G2-G3	Pain; testicular asymmetry >20%; subfertility on sperm analysis at 17 years of age	No varicocele, no reflux	87.9	One hydrocele, two wound infections, two hematomas	11 (12%)	3/91
Mazzoni ⁷	Cohort, prospective	65 (21 recurrent)	ND	9 (mean)	G3-symptomatic	G3-symptomatic	No clinical varicocele	93.3	—	5 (6.7%)	No
Mazzoni et al. ⁸	Cohort, retrospective	44	13.5	4	G3	G3	No reflux Doppler	95.5	0	2 (4.5%)	No
Mottrie et al. ⁹	Cohort, retrospective	38	14.9 (mean)	ND	G1-G3	G1-G3	No clinical varicocele	95	One epididimitis (2.5%)	2 (5%)	No
Paradiso et al. ¹⁰	Cohort, retrospective	59	14.7	14	G1-G3	G3-symptomatic-hypotrophy	No clinical varicocele	96.6	3 (4.1%) flebothrombosis	2 (3.3%)	No
Zaupa et al. ¹¹	Cohort, retrospective	88	13.3	11	G2-G3	G2-G3	No G2-G3 varicocele	93%	3 (3%)	6 (7%)	No

US; however, a minority of included articles defined success as “no reflux at US” (Table 2 for details).

Outcomes

Postoperative complication rate ranged from 1.09% to 2.5%, with four studies Fette and Mayr,³ Ficarra et al.,⁴ Mazzoni et al.^{7,8} reporting no complications at all. Complications mainly included epididymo-orchitis. In one study Keene and Cervellione,⁶ one case of hydrocele was registered. Paradiso et al.¹⁰ registered 3 cases (4.1%) of pampiniform plexus phlebothrombosis, all minor complications. In one study Zaupa et al.,¹¹ there was also a partial testicular necrosis despite correct sclerotherapy.

Results of the included studies are shown in Table 1. A satisfactory follow-up was conducted in patients who underwent surgical correction in almost all studies. The median follow-up ranged between 4 and 69 months. All the studies analyzed reported a success rate ranging from 87.9% to 97.7%.

The recurrence rate after the procedure ranged from 2.2% to 12% within 1 year follow-up. Beutner et al.² found a correlation between high varicocele grade and treatment failure that reached statistical significance ($p=0.048$). Hung et al.⁵ showed that clinical recurrence (grade 2–3) within 1 year was similar between the two groups of AS and LV with four out of 48 patients in the AS group and six out of 62 patients in the LV group (8.4% in AS vs 9.7% in LV, $p=1.00$); Mazzoni et al.⁸ obtained similar results. In one study Paradiso et al.,¹⁰ anatomical variations in Coolsaet type I varicoceles were identified and organized, where possible, using Bühren’s classification. These authors believe that, in order to further reduce the recurrence/persistence rates in the treatment of varicocele, more attention should be given to diagnosing and treating type II and III varicoceles: for this reason, phlebography should always be performed.

In one study Keene and Cervellione,⁶ 26 out of 28 patients who underwent AS for testicular asymmetry had full resolution of the asymmetry to <20% (catch-up growth) after surgery, although an improvement was seen in all 28 patients. Moreover, all 38 patients treated for pain had resolution of pain symptoms following surgery.

Technical aspects

In one study Keene et al.⁶ introduced two modifications to the technique: first, they stopped using the Y-shaped intra-venous connector between the cannula and syringe, because in their hypothesis when injecting such a small volume of sclerosant (maximum 3 ml) a significant portion remained within the connector, thus reducing its efficacy. Thus, the syringe was then connected directly to the cannula, ensuring maximum efficacy. Second, they used Aethoxysklerol as a microfoam instead of a liquid. The

preparation technique described by the manufacturer involves mixing the Aethoxysklerol with 7 ml of air and making it into a foam using a micro-foam adaptor to produce 10 ml of a stable, homogenous and viscous microfoam with fine bubbles. The viscosity of the microfoam reduces fast “run-off” into the renal vein and systemic circulation and increases the surface area and contact time between the sclerosant and vessel wall.

The main difficulty in Tauber’s procedure was found to be the cannulation of the veins. The vessels of the pampiniform plexus can be very small and fragile in childhood, so that sometimes it is tedious to cannulate a suitable vein. In one case, Mazzoni et al.⁸ had to convert local anesthesia to general anesthesia and surgery to a Palomo procedure because it was impossible to find a pampiniform plexus vein draining into the internal spermatic vein. In another study, Zaupa et al.¹¹ in 18% of cases the operators had to expose a second or third vein, and this prolonged the operation time and increased the possibility of complications afterward, such as scrotal hematoma.

Discussion

The present review shows that antegrade sclerotherapy for pediatric varicocele may have a success rate of 88%–98%, while the complication rate was <5%.

Varicocele remains a leading reversible cause of infertility in men.¹⁴ The mechanisms explaining how a varicocele interferes with sperm production are not clearly understood, and theories include: venous hyperemia, increased testicular temperature and testicular hypoxia. Pathological changes occur in Leydig and Sertoli cells, many of which improve following varicocele repair.¹⁵ In approximately 40% of all cases, varicocele is the main reason for male infertility.¹⁶ Patients with varicocele frequently complain of painful scrotal swelling. During childhood and adolescence varicoceles are usually detected by localized scrotal pain and routine examinations.

Overall, the results of the present review indicate that Tauber’s antegrade scrotal sclerotherapy is an effective method for varicocele ablation in children and adolescents which ensures minimal invasion, a low technical expense, an acceptable radiation load, and a very low complication and persistence rate.

AS is an effective minimally invasive treatment for varicocele with low recurrence/persistence rate also in adult patients. Crestani et al.¹⁷ showed that in patients with a low sperm number before surgery, sperm count improved from 13×10^6 to 21×10^6 ml⁻¹ ($p < 0.001$). The median value of the percentage of progressive motile forms at 1 h improved from 25% to 45% ($p < 0.001$). Percentage of normal forms increased from 17% before surgery to 35% 1 year after the procedure ($p < 0.001$). In the subgroup of the 168 infertile patients, 52 (31%) fathered offspring at a 12-month-minimum follow-up. A

persistent/recurrent varicocele was detected in 40 (5.9%) cases. In 32/40 (80%) cases, patients showed preoperative grade III varicoceles.

Moreover, the AS technique allows to preserve the lymphatic vessels and testicular arteries offering a very low percentage of complications without risk of hydrocele and testicular hypotrophy.¹⁷ A recent meta-analysis published by Wang et al.¹⁸ showed that AS and microsurgical repair are superior to other techniques (open retroperitoneal surgery, laparoscopic approach) in terms of hydrocele formation. In fact, the most important clinical implication of the results is the low odds of hydrocele formation using minimally invasive procedures like Tauber antegrade sclerotherapy and embolization compared to other techniques.¹⁹ The most common complications were scrotal hematoma and epididymo-orchitis. One case of partial testicular necrosis was registered.

The patients treated had clinically relevant improvement in local pain and/or resolution of testicular asymmetry and sperm test parameters. Testicular catch-up growth was higher with AS as compared to other techniques. A meta-analysis by Silay et al.²⁰ reported that testicular catch-up growth rates after interventional varicocele treatment (antegrade sclerotherapy, retrograde embolization, etc.) were between 86% and 100%. Following laparoscopic varicocelectomy, it was reported between 77% and 100%, whereas following open varicocelectomy (subinguinal, inguinal, Palomo, microscopic, etc) it was between 62.8% and 97.1%. Total sperm concentration was also increased in children who underwent intervention compared with observation. Sperm tests, in most of the patients of the study by Crestani et al.,¹⁷ including adolescents and adults, showed an increase of the percentage of normal sperm cell forms and 31% of patients fathered offspring at a 12-month-minimum follow-up. It was demonstrated that all parameters were increased after interventional, microscopic, and laparoscopic treatments.^{6,21–24}

Because of the anatomy in children, cannulation of the chosen vein can be more difficult, and the surgery tends to be longer than in adults. As a rare complication, localized testicular damage can occur despite correct treatment.¹¹ Hung et al.⁵ excluded two patients because of abnormal venous drainage found on pre-sclerotherapy antegrade venogram. Anomalous venous drainage is reported in up to 15% of patients in the literature.¹² For patients who have anomalous drainage, antegrade sclerotherapy is generally not advised, as an incorrect cannulation of superficial vein of spermatic cord or presence of abnormal venous anatomy could be responsible for relevant complications because of occlusion and/or chemical damage of veins in other body districts.¹⁷

The present study is not devoid of limitations. All included studies are monocentric series, mostly retrospective, and this could be a potential source of bias. Moreover, the inclusion criteria varied between studies, as did the

definition of success, and this could hinder the comparison of results among different series. Finally, no meaningful conclusions can be drawn about the role of sperm analysis, as a small minority of patients had this information available.

The EAU/ESPU guidelines for pediatric varicocele do not provide indications about treatment modalities, but they recommend active treatment during the pediatric/adolescent age (in absence of reliable sperm analysis) only in case of reduced testicular volume on the affected side (difference >20% or 2 ml). On the other hand, the treatment should be weighted on a case-by-case setting in other situations such as local symptoms, contralateral conditions potentially affecting the fertility and cosmetic concerns. For these reasons, we believe that further comparative studies among different treatment should be based on standardized, guideline-based inclusion criteria.

In conclusion, AS is a suitable technique for varicocele treatment in pediatric patients, with good success rate and rare complications, and could therefore be considered among the procedures of choice in this setting. Further prospective studies would be needed to compare the results of AS with other techniques, as well as provide potential predictive factors for success or failure of each procedure.

Authors' contribution

Conceptualization: AM, MB, PB, MM, MI, FDM, literature search and data collection: GA, AM, GM, MB., manuscript writing: GA, GM, AM, FZ, MB.; writing—review and editing: all authors, supervision: AM and FDM. All authors have read and agreed to the published version of the manuscript.

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