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Embolization in Juvenile Nasopharyngeal Angiofibroma Surgery: A Systematic Review and Meta-Analysis

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Objective: To compare outcomes of juvenile nasopharyngeal angiofibroma (JNA) resection between embolized and non-embolized cohorts, and between transarterial embolization (TAE) and direct puncture embolization (DPE).

Data Sources: Per PRISMA guidelines, PubMed, Embase, Web of Science, Scopus, and Cochrane databases were searched for publications prior to or in 2021.

Materials and Methods: Original English manuscripts investigating the resection of JNA with and without preoperative embolization were included. Embolization type, recurrence rate, complication rates, blood loss, and transfusions were extracted. Risk of bias was assessed by the Risk of Bias in Non-randomized Studies—of Interventions method.

Results: There were 61 studies with 917 patients included. Preoperative embolization was performed in 79.3% of patients. Of those embolized, 75.8% ($N = 551$) underwent TAE and 15.8% ($N = 115$) underwent DPE. JNA recurrence in embolized patients was lower than in non-embolized patients (9.3% vs. 14.4%; odds ratio [OR]: 0.61, 95% confidence interval [CI]: 0.35, 1.06). DPE resulted in lower rates of disease recurrence (0% vs. 9.5%; OR: 0.066, 95% CI: 0.016, 0.272) and complications (1.8% vs. 21.9%; OR: 0.07, 95% CI: 0.02, 0.3) than TAE. A random effects Bayesian model was performed to analyze the difference in mean blood loss in 6 studies that included both embolized and non-embolized patients. This analysis showed a mean reduction in blood loss of 798 mL in the embolized group.

Conclusions: We found embolization decreases blood loss in JNA resection. DPE led to improved recurrence and complication rates when compared to TAE, but future prospective studies are needed to further evaluate which embolization technique can optimize outcomes in JNA.

Key Words: juvenile nasopharyngeal angiofibroma, embolization, transarterial embolization, direct embolization.

Level of Evidence: NA

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INTRODUCTION

Juvenile nasopharyngeal angiofibroma (JNA) is a benign, highly vascular tumor with an incidence of 1:150,000.[1,2] Due to hormonal and genetic factors, it commonly presents in young boys and adolescent males, ages 9–19, with rare cases occurring in adult men and women.[3–5] These neoplasms typically originate near the basisphenoid and superior margins of the sphenopalatine foramen and expand with destructive growth into the nasal cavity, nasopharynx, paranasal sinuses, orbit, and skull base.[6,7] JNA patients present with the triad of epistaxis, unilateral nasal obstruction, and a nasopharyngeal mass.[8]

Due to their aggressive and destructive growth pattern and anatomic location, JNAs may have significant morbidity.[9] JNAs can be cured through surgical excision, with endoscopic approaches preferred over open approaches,[10] but these procedures carry a risk of hemorrhage which renders the management of these tumors inherently more complicated.[7]

One method which serves to reduce blood loss during surgical extirpation is tumor embolization. Many case studies show embolization is effective in reducing blood flow to tumors and some suggest it improves overall outcomes.[11,12] Whether embolization is a beneficial addition to the surgical strategy of JNAs is controversial, however, with some literature emphasizing that embolization distorts the tumor boundaries and may contribute to incomplete resection of the tumor and higher rates of tumor recurrence.[12,13] Despite this controversy, most authors

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endorse embolization, citing a decrease in blood loss and the avoidance of blood transfusions during and after surgery.[14,15]

Direct puncture embolization (DPE) has been shown to provide easy access to hypervascular tumors with a higher chance of achieving devascularization compared to indirect transarterial embolization (TAE).[16] Because of the rarity of JNA, is it difficult for single-center cohort studies to demonstrate whether TAE or DPE affects blood loss, tumor recurrence, and complication rates.

Although transnasal endoscopic resection of JNA is widely established, the safety and efficacy of preoperative tumor embolization are not clearly defined. In addition, the embolization technique that is most beneficial has yet to be definitively understood. Thus, the questions this analysis aims to further answer are two-fold: whether preoperative embolization improves outcomes in operative management of JNA, and, if so, which technique is more favorable. We hypothesize that preoperative embolization significantly reduces patient blood loss and improves overall outcomes of surgical treatment of JNA, with the DPE technique being superior at doing so to the TAE technique.

MATERIALS AND METHODS

Literature Search

The PubMed/Medline, Cochrane, Embase, Scopus, and Google Scholar databases were systematically screened on December 21, 2021, using Medical Subject Headings (MeSH) and terms, the details of which are included in supplemental materials.[17] A medical librarian (SMS) developed a comprehensive search strategy and applied it to all aforementioned databases. The MeSH terms "angiofibroma" and "nasopharynx" were used with words such as "JNA," "juvenile nasopharyngeal angiofibroma," and "pediatric/child/adolescent" filter terms. The search was limited to articles written in English between the inception of the databases and 2021. The initial search yielded 1959 total citations, with 1310 duplicates removed, resulting in 649 individual studies. Of the initial 649 studies screened, 408 were not relevant to our study aims, 179 either did not have full texts, were strictly qualitative (commentaries, editorials), were written in a language other than English, or did not contain any of our variables of interest, resulting in 61 studies that were included in the final analysis and reported according to PRISMA guidelines (Fig. 1).

Selection Criteria

Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was utilized for article screening. Manuscripts investigating surgical resection of JNA with or without preoperative embolization were included. Reviews, meta-analyses, and non-English studies were excluded. All studies were independently assessed by two researchers (AD, EW) who determined whether to include/exclude each study. Each title, abstract, and full-text article was categorized by each of the two researchers into "include" or "exclude" independently. Inclusion/exclusion conflicts were resolved by the principal investigator (CRR). All study designs with original data and cases were included (Fig. 1).

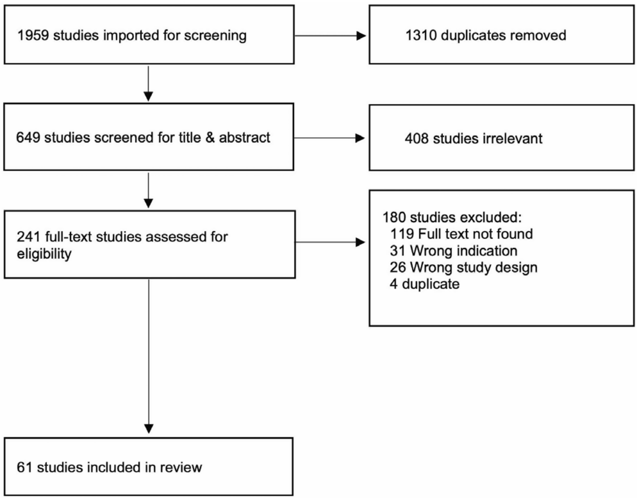

Fig. 1. PRISMA flowchart for selection of studies.

Data Extraction

Studies that met inclusion criteria were analyzed using the same data extraction sheet. Study descriptive information, design, sample size, embolization prevalence and type, procedure type, recurrence, blood transfusions, complications, and study quality were extracted into a Microsoft Excel, Version 16.63.1 (Microsoft Corporation, 2018) document by four researchers (AD, EW, DB, TC) and any differences were resolved by the principal investigator (CRR). Study characteristics were reported in Table I.

Statistical Analysis

We performed both qualitative and quantitative analyses. First, frequencies of data extraction variables were calculated and descriptively reported. Due to the heterogeneity of the studies, a formal meta-analysis to evaluate differences in recurrence outcomes between embolized and non-embolized patients was not possible. Further, quantitative meta-analysis to assess differences in outcomes between TAE and DPE was also not possible within the limitations of the studies included. Therefore, pooled analyses were performed to report on these outcomes. There was sufficient data to perform random and common effect Bayesian meta-analysis comparing mean blood loss between embolized and non-embolized patients described in a subset of 6 included studies. Analyses were performed using R package meta according to Balduzzi et al.[77] Transformations of median/range into mean/SD were created according to Hozo et al.[78] and a $p < 0.05$ was considered statistically significant.

Risk of Bias Assessment

To assess the risk of bias in each of the studies, we employed the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool developed for evaluating the risk of bias in estimates of the comparative effectiveness of interventions.[79] Two researchers (AD and EW) independently reviewed all studies and rated them on defined scales according to the ROBINS-I which included ratings of low, moderate, serious, critical, and not indicated.[79] The categories for which the studies were graded are displayed in Table II and a visualization of bias across seven domains is displayed in Fig. 2 according to Risk-of-

TABLE I.
Study Characteristics.

Author (Year)	Study Design	Number of Participants	% Male	Age (Mean, SD)	Embolization Performed: Number of Patients Embolized	Embolization Performed: Number of Patients Non-Embolized	Type of Embolization: DPE	Type of Embolization: TAE	Type of Embolization: Number of Complications Reported
Ahmad (2008)	Case series	5	100	15, 2.1	0	5	NA	NA	0
Ahmed (2020)	Case series	35	100	19, 3.5	35	0	0	35	0
Amran (2019)	Case series	5	100	23, 21	4	1	0	4	0
Aziz-Sultan (2011)	Case report	1	100	13	1	0	1	0	0
Ballah (2013)	Case series	17	100	14, 2.2	17	0	0	17	3
Baradaranfar (2003)	Case series	16	100	16, 2.1	13	3	NR	NR	0
Beckmann (2019)	Case report	1	100	10	1	0	1[a]	1[a]	0
Natvig (1984)	Case report	2	100	16	2	0	0	2	NR
Bleier (2009)	Case series	18	100	17	18	0	NR	NR	0
Desarda (1998)	Case series	9	100	NR	5	4	0	5	0
Edner (1982)	Case report	1	100	15, 3.4	1	0	NA	1	0
El-Banhawy (2006)	Case series	20	100	15	0	20	NA	NA	2
Elhammady (2011)	Case series	10	100	NR	10	0	5	5	0
Elmokadem (2017)	Case series	20	100	15, 7.2	20	0	0	20	7
Fonseca (2008)	Case series	15	100	19, 5.1	0	15	NA	NA	3
Gao (2013)	Case series	50	100	NR	50	0	11	39	0
Garcia-Cervigon (1988)	Case series	51	100	17, 4.2	51	0	0	51	3
Gargula (2021)	Case series	92	100	18.3	14	78	0	14	0
Gemmete (2010)	Case series	6	100	16.7	6	0	6	0	0
Gemmete (2011)	Case report	1	100	17	1	0	1	0	0
Gemmete (2012)	Case series	9	100	15	9	0	9	0	0
Gore (2008)	Case series	3	100	14, 5.8	3	0	0	3	0
Gruber (2000)	Case series	7	100	14.5, 4.9	7	0	0	7	0
Herman (2011)	Case series	4	100	13.5	4	0	4	0	1
Hira (2011)	Case report	1	100	16	1	0	1	0	0
Ikawa (1984)	Case report	2	100	14.5, 2.5	1	1	0	1	0
Janakiram (2016)	Case report	1	100	20	1	0	0	1	1
Jang (2013)	Case report	2	100	25, 5	2	0	2	0	0
Kasem (2016)	Case series	29	100	14, 4	29	0	29	0	0
Katsiotis (1979)	Case series	4	100	15.5	4	0	0	4	NR
Khoury (2017)	Case series	4	100	21	1	0	0	1	1
Krstulja (2008)	Case report	1	100	52	1	0	1	0	NR
Li (1998)	Case series	21	100	20.2	11	10	0	11	1
Lutz (2016)	Case series	15	100	15.6, 6.9	15	0	7	10	3
Lv (2013)	Case series	22	100	16, 3.2	22	0	22[a]	22[a]	5
Maroda (2020)	Case report	1	100	10, 0.5	1	0	1[a]	1[a]	0
Mishra (2019)	Case report	1	100	9	1	0	NA	1	0

(Continues)

TABLE I.
Continued

Author (Year)	Study Design	Number of Participants	% Male	Age (Mean, SD)	Embolization Performed: Number of Patients Embolized	Number of Patients Non-Embolized	Type of Embolization: DPE	TAE	Number of Complications Reported
Mohammadi (2010)	Randomized controlled trial	23	100	16.6	9	14	0	9	2
Morishita (2020)	Case report	1	100	23	0	1	0	0	0
Moulin (1995)	Case-control study	20	100	14.7, 3.4	13	9	0	13	0
Ogawa (2012)	Case series	170	100	13.6	170	0	0	170	79
Önerci (2005)	Case report	1	100	12	1	0	0	1	1
Palmer (1989)	Case series	12	91.7	15, 4.12	12	0	0	12	0
Pamuk (2018)	Cross-sectional study	48	100	NR	30	18	NR	NR	NR
Parikh (2014)	Case report	1	100	32	1	0	0	1	0
Pedicelli (2020)	Case series	1	100	17	1	0	1	0	0
Pei (2019)	Case-control study	27	100	21.9	17	10	0	17	0
Petruson (2002)	Case series	32	100	17.5	20	12	0	20	NR
Pletcher (1975)	Case-control study	23	100	15.1	7	16	0	7	NR
Roberson (1972)	Case series	4	100	14	4	0	0	4	NR
Romani (2010)	Case report	1	100	17	1	0	1[a]	1[a]	1
Rosenbaum-Halevi (2020)	Case series	9	100	14.1, 6.3	9	0	0	9	1
Santaolalla (2009)	Case-control study	8	100	16.5, 2.4	4	4	0	4	NR
Santos-Franco (2012)	Case report	1	100	14	1	0	0	1	0
Schroth (1996)	Case series	4	100	15, 1	4	0	0	4	NR
Shenoy (2002)	Case series	30	100	19	30	0	0	30	1
Siniluoto (1993)	Case series	10	100	14, 2.4	4	6	0	4	NR
Tan (2017)	Randomized controlled trial	74	98.6	24, 5.9	32	42	0	32	0
Tang (2009)	Case series	13	100	17	13	0	0	13	NR
Tawfik (2018)	Case report	1	100	13	1	0	0	1	1
Tranbahuy (1994)	Case series	7	100	15	7	0	0	7	NR

Note: All studies cited within the References 11,12,18–76.
DPE = direct puncture embolization; NA = not applicable; NR = not reported; TAE = trans-arterial embolization.
[a]Both embolization techniques used.

bias VISualization (robvis) online tool.[80] Differences were assessed and resolved by an independent third researcher (DB).

RESULTS

Study Characteristics

There were 61 studies included (Fig. 1, Table I). Study designs included case reports (19, 30.6%), case series (including case-controlled, retrospective, and prospective) (41, 66.1%), and randomized controlled trials (2, 3.2%). Of the 61 studies included in this review, 23% ($n = 14$) displayed a moderate level of bias according to the ROBINS-I rating whereas the remaining 77% ($n = 47$) displayed a mild level of bias (Table II, Fig. 2). There were 917 total patients recorded across all studies with population sizes ranging from $n = 1$ to 170. For studies in which data were reported and available ($n = 747$), the mean age was 15.8 years old and 99.8% ($N = 745$) were male. There was inadequate data and heterogeneity in reporting of race, so no analysis of race could be performed.

TABLE II.
Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) Risk Bias Assessment across seven Domains According to a Scale of Mild, Moderate, and Severe.

	Bias Type							
Study	Confounding	Selection	Classification of Interventions	Deviation from Intended Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Result	Overall
Ahmad (2008)	Moderate	Low	Low	Low	Low	Low	Low	Low
Ahmed (2020)	Low	Low	Low	Low	Low	Low	Low	Low
Amran (2019)	Moderate	Low	Low	Low	Low	Low	Moderate	Low
Aziz-Sultan (2011)	Low	Low	Low	Low	Low	Low	Serious	Moderate
Ballah (2013)	Moderate	Low	Low	Low	Low	Moderate	Low	Low
Baradaranfar (2003)	Low	Low	Low	Low	Serious	Moderate	Moderate	Moderate
Beckmann (2019)	Low	Low	Low	Low	Low	Low	Moderate	Low
Natvig (1984)	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate
Bleier (2009)	Low	Low	Low	Low	Low	Low	Moderate	Low
Desarda (1998)	Moderate	Low	Moderate	Low	Moderate	Low	Moderate	Moderate
Edner (1982)	Low	Low	Low	Low	Low	Low	Low	Low
El-Banhawy (2006)	Low	Low	Low	Low	Low	Low	Low	Low
Elhammady (2011)	Low	Low	Moderate	Low	Low	Low	Low	Low
Elmokadem (2017)	Low	Moderate	Low	Low	Low	Low	Low	Low
Fonseca (2008)	Low	Moderate	Moderate	Low	Low	Low	Low	Low
Gao (2013)	Low	Low	Low	Low	Low	Low	Low	Low
Garcia-Cervigon (1988)	Low	Moderate	Serious	Low	Low	Moderate	Moderate	Moderate
Gargula (2021)	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Gemmete (2010)	Low	Moderate	Low	Low	Low	Moderate	Low	Low
Gemmete (2011)	Low	Low	Low	Low	Low	Low	Low	Low
Gemmete (2012)	Low	Low	Low	Low	Low	Low	Low	Low
Gore (2008)	Moderate	Low	Low	Low	Low	Low	Low	Low
Gruber (2000)	Low	Low	Low	Low	Low	Low	Low	Low
Herman (2011)	Low	Moderate	Low	Low	Low	Low	Low	Low
Hira (2011)	Low	Moderate	Low	Low	Low	Low	Low	Low
Ikawa (1984)	Low	Moderate	Low	Low	Low	Low	Low	Low
Janakiram (2016)	Low	Moderate	Low	Low	Low	Low	Low	Low
Jang (2013)	Low	Moderate	Low	Low	Low	Low	Low	Low
Kasem (2016)	Low	Low	Low	Low	Moderate	Low	Low	Low
Katsiotis (1979)	Moderate	Moderate	Low	Low	Serious	Serious	Low	Moderate
Khoury (2017)	Low	Low	Low	Low	Low	Low	Serious	Low
Krstulja (2008)	Low	Moderate	Low	Low	Low	Low	Low	Low
Li (1998)	Moderate	Moderate	Low	Low	Low	Low	Moderate	Low
Lutz (2016)	Moderate	Low	Low	Low	Low	Low	Low	Low
Lv (2013)	Low	Low	Moderate	Low	Low	Low	Low	Low
Maroda (2020)	Low	Moderate	Low	Low	Low	Low	Moderate	Low
Mishra (2019)	Low	Moderate	Low	Low	Low	Low	Moderate	Low
Mohammadi (2010)	Moderate	Low	Low	Low	Low	Low	Low	Low
Morishita (2020)	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Moulin (1995)	Moderate	Low	Low	Low	Low	Low	Low	Low
Ogawa (2012)	Moderate	Low	Low	Low	Low	Low	Low	Low
Önerci (2005)	Low	Moderate	Low	Low	Low	Low	Low	Low
Palmer (1989)	Low	Low	Low	Low	Moderate	Low	Low	Low
Pamuk (2018)	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Parikh (2014)	Low	Low	Low	Low	Low	Low	Low	Low
Pedicelli (2020)	Low	Low	Low	Low	Low	Moderate	Low	Low
Pei (2019)	Low	Low	Low	Low	Low	Low	Low	Low

(Continues)

TABLE II.
Continued

Study	Bias Type							
	Confounding	Selection	Classification of Interventions	Deviation from Intended Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Result	Overall
Petruson (2002)	Low	Moderate	Low	Low	Low	Low	Low	Low
Pletcher (1975)	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Roberson (1972)	Moderate	Moderate	Moderate	Low	Serious	Moderate	Low	Moderate
Romani (2010)	Low	Moderate	Low	Low	Low	Low	Low	Low
Rosenbaum-Halevi (2020)	Low	Low	Low	Low	Low	Low	Moderate	Low
Santaolalla (2009)	Low	Moderate	Low	Low	Low	Low	Low	Low
Santos-Franco (2012)	Low	Low	Low	Low	Moderate	Moderate	Low	Low
Schroth (1996)	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
Shenoy (2002)	Low	Low	Low	Low	Moderate	Low	Low	Low
Siniluoto (1993)	Low	Low	Low	Low	Low	Low	Low	Low
Tan (2017)	Low	Low	Low	Low	Low	Low	Low	Low
Tang (2009)	Moderate	Moderate	Serious	Low	Moderate	Moderate	Low	Moderate
Tawfik (2018)	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
Tranbahuy (1994)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Low

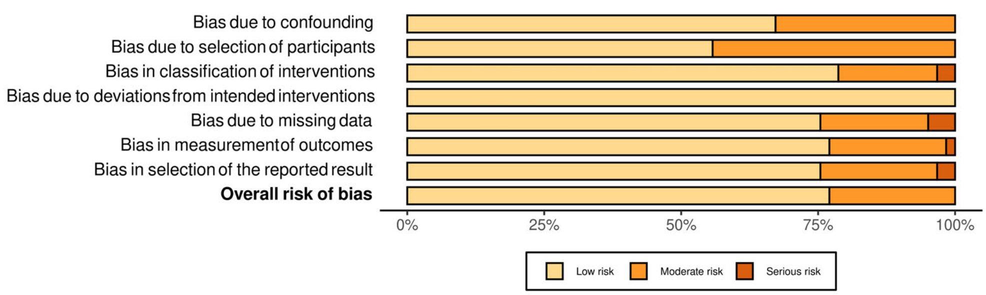

Fig. 2. Visualization of bias across seven domains according to Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Embolization Information

Preoperative embolization, which included DPE, TAE, or a combination of the techniques, was performed in 79.3% ($n = 728$) of patients (Table I). Types of DPE included: direct percutaneous embolization and embolization with onyx in conjunction with particulate (ethylene-vinyl alcohol copolymer). Types of TAE included: transarterial gel foam, traditional transarterial onyx, transarterial particulate embolization, transcatheter arterial embolization, and endovascular particulate embolization. Of those embolized and with the type of embolization information available ($n = 691$), 79.7% ($n = 551$) had TAE, 16.6% ($n = 115$) had DPE, and 3.6% ($n = 25$) had both TAE and DPE. Specifically analyzing non-embolized patients with procedure information available ($n = 155$), 58.1% ($n = 90$) had endoscopic surgery and 41.9% ($n = 65$) had open surgery. There were 438 embolized patients with procedure information available and of those, 63.2% ($n = 277$) had endoscopic surgery, 36.3% ($n = 159$) had open surgery, and 0.5% ($n = 2$) had combined approaches. There was insufficient data to examine the specific timing of embolization prior to surgery.

Clinical Outcomes

Disease recurrence. The average follow-up time was 28.5 months (range 2–168). Only 4 studies of non-embolized patients reported follow-up times, with an average of 51.3 months (range 10–120). There were 23 studies of embolized patients that reported follow-up data, with an average of 22.9 months (2–144 months). JNA recurrence in embolized patients was lower in comparison to non-embolized patients (9.3% vs. 14.4%). Of patients undergoing DPE, 74 had available recurrence data. There were no recurrences reported in this cohort. Of patients undergoing TAE, 452 had recurrence data available with 43 recurrences (9.5%) reported. Those undergoing DPE were less likely to have a recurrence than those undergoing TAE in this dataset (odds ratio [OR]: 0.07 95%, confidence interval [CI]: 0.02, 0.27).

Blood loss. In comparing 391 embolized patients and 99 non-embolized patients with intraoperative blood loss data, average blood loss was significantly lower in embolized patients (842 mL vs. 1525 mL, $p < 0.01$). When comparing DPE and TAE patients for which blood loss

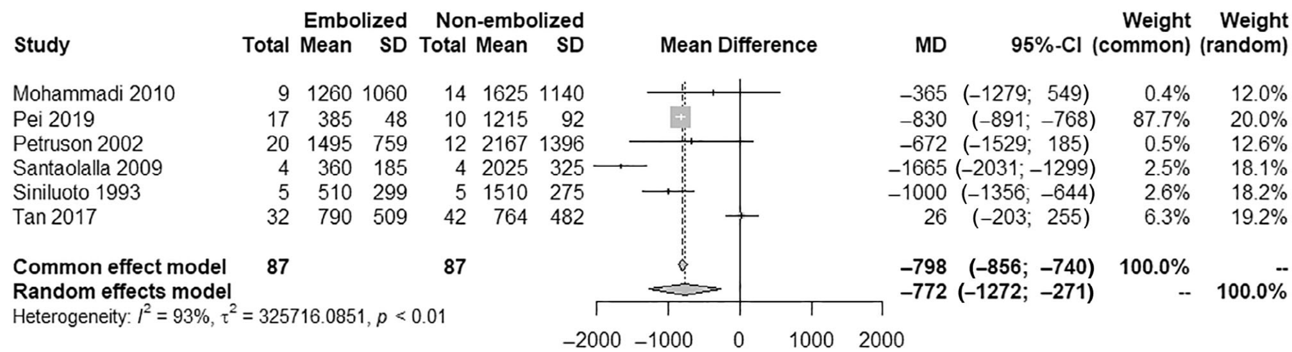

Fig. 3. Forest Plot of six studies that assessed both embolized and non-embolized patients while also reporting estimated blood loss. We estimated a mean additional blood loss of 798 mL (740 and 856 mL) in the random effects model.

data was reported ($n = 367$), the average blood loss during surgery was similar between the two techniques (779 mL for DPE compared to 864 mL for TAE). From the available data evaluating embolization and blood transfusions, 22.7% ($n = 44/194$) of patients receiving embolization had a blood transfusion during or after JNA surgery wheras 38.8% ($n = 26/67$) of non-embolized patients had reported blood transfusions (OR: 0.45, 95% CI: 0.63). When comparing DPE and TAE, 6.7% ($n = 2/30$) of DPE had a blood transfusion and 34.4% ($n = 42/122$) of TAE underwent transfusion (OR: 0.14, 95% CI: 0.53). A Bayesian meta-analysis of six studies that compared both embolized and non-embolized patients which also supplied the estimated blood loss amount and variation for each group was created as a Forest Plot (Fig. 3). We estimated a mean additional blood loss in the non-embolized cohort of 798 mL (740 and 856 mL) in the random effects model and 772 mL (271 and 1272 mL) in the common effects model (Fig. 3).

Postoperative Complications. Of the cohort with available data regarding other postoperative complications ($n = 684$), 80.6% ($n = 523$) had no complications reported. Nineteen percent of patients ($n = 116$) had complications, most of which were neurological such as oculomotor nerve palsy or cerebrospinal fluid leaks, others of which included anemia or post-operative bleeding requiring transfusion. Most of these complications were temporary. Within the embolized cohort, 19.3% ($n = 108/561$) reported complications whereas within the non-embolized cohort, 6.6% ($n = 8/122$) reported complications. DPE had a lower rate of complications than TAE, 1.8% ($n = 2/110$) versus 21.9% ($n = 99/452$), respectively (OR: 0.07, 95% CI: 0.02, 0.3). No deaths related to JNA resection were reported.

DISCUSSION

This qualitative analysis is the most comprehensive to date and pools data from 61 studies and 917 patients to assess outcomes associated with JNA resection with and without preoperative embolization. Moreover, a formal Bayesian meta-analysis was possible to be performed on a subset of 6 studies and 84 patients, which showed a statistically and clinically significant decrease in blood loss in the preoperative embolization group. This is the first study to compare outcomes in patients undergoing DPE and TAE. Although no formal quantitative analysis could be performed due to study heterogeneity and lack of sufficient data, qualitative analysis suggests that DPE may lead to improved blood loss outcomes and reduced complications compared to TAE. The data herein are particularly important, as there remains little consensus as to the need for embolization, and whether a direct or transarterial approach to embolization should be performed. Our results underscore the need for higher quality, prospective, and likely multi-institutional studies to more adequately evaluate differences in outcomes between the two embolization techniques.

Embolization and Recurrence Rates

Analyzing recurrence rates with respect to any tumor can be a complicated task given there are many factors that can influence tumor recurrence. One article analyzing recurrence rates in JNA specifically found that in 97 patients, 39.2% ($n = 38$) experienced recurrence, most of which occurred within the first 12 months after the operation and a minority occurring after 2 years postoperatively.[81] Several factors can affect this rate in JNA including patient age, tumor size, procedure type, and possibly the use of preoperative embolization. Although we did not have the ability to control for these factors given this was a pooled dataset with a lack of complete demographic and clinical data, we nonetheless found that patients undergoing embolization were less likely to experience recurrence, which is consistent with previous literature.[82] This finding was in the context of an average follow-up time of 28.5 months for all studies, 51.3 months for non-embolized studies, and 22.9 months for embolized studies. Compared to a recurrence rate of (14.4%, $n = 20$) in the non-embolized group, the recurrence rate in the TAE cohort was 9.5% ($n = 43$), and the recurrence rate was zero in the DPE cohort. Although the mean follow-up times reported in the non-embolized group were longer than the embolized groups, the studies reporting on recurrence rates in the embolized groups included for analysis did have a mean follow-up of 22.9 months, which is nearly double the 12-month range in which most of these tumors recur, and thus the risk of a significant underestimate of recurrence rate is low.[81] Moreover, there was limited and heterogeneous data available with regard to tumor extent or stage, and therefore none of the accepted staging systems could be utilized to evaluate the effects of disease extent on recurrence rates. Although the difference in follow-up data and missing data may limit this study's attempts to compare recurrence in non-embolized and embolized groups, the findings herein suggest that embolization may reduce the risk of tumor recurrence regardless of the technique performed and that an even larger recurrence risk reduction may exist with DPE compared to TAE. We hypothesize that recurrence rates could be lower with embolization as a greater portion of the tumor can be resected due to improved intraoperative visualization and decreased concern for uncontrolled bleeding. The decreased recurrence risk with DPE compared to TAE may be due to improved vascular control of tumors utilizing this technique, although further studies that attempt to control for tumor size, stage, and origin of feeding vasculature will be necessary to definitively comment on the benefits of DPE compared to TAE.

Embolization and Blood Loss

Given that JNAs are highly vascularized tumors that reside in challenging anatomic areas such as the pterygopalatine fossa, infratemporal fossa, and posterior nasopharynx, it is inevitable that bleeding will occur during surgical resection.[4] Histologically, JNAs show varying sizes of thinly-lined vascular channels, often consisting of one layer of endothelium without a muscular layer.[3,10] It has been well documented that extensive blood loss during resection is frequently encountered during JNA removal, which may lead to injury to surrounding structures and incomplete resection.[18,83] Both the qualitative pooled analysis and formal Bayesian meta-analysis showed that preoperative embolization led to both clinically and statistically significantly reduced intraoperative blood loss, although blood loss was similar when comparing embolization techniques. Moreover, the percentage of patients requiring blood transfusions was lower for embolized patients (44/194, 22.7% vs. 26/67, 38.8%), and the rate of transfusion was noted to be lower for DPE compared to TAE. Although prior studies have suggested that DPE may result in lower blood loss, many of these studies did not reach significance, likely due to underpowering in the setting of a rare tumor and a small study size.[19] Our results suggest that blood loss is not significantly different within embolization types but is significantly reduced in embolized patients compared to non-embolized patients. Thus, although further studies should be performed to analyze differences in blood loss between embolization techniques, the data herein support a statistically and clinically significant reduction in blood loss and transfusion for patients with JNA undergoing preoperative embolization.

Embolization and Complications

Although the overall complication rate of endoscopic approaches to JNA is low and more data are needed to fully assess complication rates comparing embolized and non-embolized cohorts,[15] our data suggest that preoperative embolization does not lead to lower overall complication rates. This is surprising because less blood loss should equate to a better surgical field which would reduce the risk of complications. This discrepancy could be explained by variations in reporting of complications in the literature and the possibility that tumors undergoing embolization may have been more complex than those in the non-embolized cohort. Additionally, embolization studies did not distinguish whether reported complications were a direct result of embolization or tumor resection. Unfortunately, due to the heterogeneity of reporting, no subgroup analysis could be performed to assess for complication rates with regard to patient and tumor-specific characteristics.

In this analysis, DPE had a significantly lower rate of complications than TAE. It has been well-documented that TAE can lead to complications due to the presence of extracranial-to-intracranial anastomoses that can inadvertently be embolized during the procedure.[11,15,20] These anastomoses could increase the likelihood of migration of embolization materials into intracranial vasculatures, specifically the ophthalmic artery, inferolateral trunk, and meningohypophyseal trunk.[84,85] This can result in poor outcomes such as blindness, stroke, or cranial nerve palsies.[86,87] Although there have been conflicting reports of complication rates for both embolization techniques in the literature, serious complications such as retinal artery occlusion and cerebral emboli have been reported with both techniques, suggesting that the risks of embolization must be considered when determining if the procedure will be performed, regardless of the technique being utilized.[15,88] Nevertheless, DPE with liquid embolization agents is anatomically less likely to leak into extracranial-to-intracranial anastomoses.

The possibility of complications due to embolization can be explained by the fact that 30%–40% of JNA blood supply is bilateral, meaning several arterial feeders need to be properly embolized in preparation for surgery.[86,87] Promisingly however, past major complications associated with DPE led to modifications to the procedure to make it safer, which include a diagnostic angiogram to identify arterial feeders and the injection of contrast agents and careful imaging to properly identify dangerous anastomoses.[89,90]

In general, the majority of embolization complications are minor. The most common complications reported for TAE were transient eye pain, cranial nerve palsies that resolved, and one case of a postoperative subdural hematoma.[21–23] Despite the risks inherent to embolization, both the TAE and DPE techniques have been shown to be safe and effective for reducing intraoperative blood loss and transfusions in vascular pathologies.[11,12,14,15]

Transarterial and Direct Puncture Embolization

TAE techniques are the traditional preoperative embolization performed by most neurointerventionalists. Although this method can provide satisfactory outcomes, there are some disadvantages to TAE approaches. Firstly, complex and large vascular tumors have numerous feeder arteries and access to the vascular tumor bed is not always possible due to small vessel diameters, tortuous arterial access, unfavorable angles, and/or vasospasm.[91] In addition, collateral feeders also play a role in feeding the tumor once the main feeders are successfully occluded and this could lead to further challenges in achieving complete embolization. DPE has emerged as a different method, though its efficacy compared to standard techniques remains controversial, especially because this technique is mostly limited to large volume centers.[90,92] Some have reported the use of both methods used in tandem, with DPE occurring before TAE, but this combined technique has been limited to a small number of complex cases.[91]

Both the literature reviewed in this analysis and studies from the neuro-intervention literature seem to advocate for DPE when possible and available as it results in less blood loss and more tumor devascularization, but DPE has not been definitively shown to be superior to TAE.[19,23,24,84] Some smaller studies have shown marginal to no significant difference between both techniques in terms of blood loss or complication rates.[11,15,23] A common trend found in studies has been that DPE trends toward lesser blood loss in comparison to TAE, but the statistical significance has not been achieved.[19,24] Although many studies have focused on clinical outcome-based measures to evaluate both techniques, others have reported on procedural delivery measures such as fluoroscopic and procedural times. These studies found that DPE has significantly shorter times for the aforementioned measures and is thus becoming preferred to TAE.[93]

Limitations and Conclusions

There are several limitations inherent to any systematic review and qualitative analysis. Firstly, there was inconsistency in available data that limited the analyses. Many older studies included cases with very little demographic information, or a lack of clinical outcome details such as the amount of blood loss, recurrence rate with adequate follow-up time, or type of embolization performed. These inconsistencies in reporting across the literature led to the exclusion of potential data points. The limited quality of data was a consequence of many case reports and case series pooling participants' data, but this limitation must be understood within the context of a very rare pathology. Additionally, our clinical question does not lend itself well to a large prospective study due to the ethical constraint, of withholding embolization in study participants, when it is widely believed to lead to better outcomes. Secondly, there was heterogeneity in surgical procedures performed in this pooled analysis which may affect the outcome parameters. There was limited data with respect to tumor characteristics such as size or location, which limits one's ability to interpret the clinical outcomes described in this analysis. Lastly, the majority of included patients underwent TAE, and the included studies did not have sufficient data regarding the length of follow-up in the TAE and DPE subgroups, which limits our ability to compare recurrence between embolization techniques. Finally, due to the limitation of data quality and significant heterogeneity among studies, formal meta-analyses could not be performed to quantitatively evaluate some of our hypotheses, such as differences in recurrence rates between embolized and non-embolized patients, and differences in outcomes between DPE and TAE.

Although the limitations of this study are notable, this systematic review is the most comprehensive to date, pooling data to achieve a large cohort of patients from which to analyze the effects of embolization and compare the efficacy of DPE and TAE. The available data supports a statistically and clinically significant mean reduction in blood loss when preoperative embolization is employed, regardless of technique. Moreover, this analysis is the first to our knowledge that attempts to compare TAE and DPE, and provides qualitative evidence to suggest that DPE may result in lower transfusion rates, decreased recurrence rates, and decreased complications compared to traditional TAE. These findings strengthen the idea that all patients undergoing JNA resection should have preoperative embolization and provide the basis for further prospective studies to elucidate which embolization technique may be best to optimize outcomes in JNA management.

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