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ORIGINAL ARTICLE

Assessment of postoperative pain in children following sclerotherapy of vascular malformations: a retrospective single centre cohort study

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BACKGROUND Inadequately controlled postprocedural pain following sclerotherapy in patients with vascular malformations is a well recognised problem. Reliable epidemiological data and risk factors associated with postprocedural pain in children are lacking.

OBJECTIVES To evaluate and quantify postprocedural pain in children and identify possible risk factors based on characteristics of the patient, treatment, and medication.

DESIGN A retrospective single centre cohort study.

SETTING A tertiary single centre study in the Netherlands.

PATIENTS Two hundred and nine chiuldren with 'simple' subtypes of congenital vascular malformation who had undergone sclerotherapy.

PRIMARY OUTCOME MEASURE Quantifying inadequately controlled postprocedural pain.

SECONDARY OUTCOME MEASURES Identifying potential patient and treatment characteristics associated with inadequately controlled postprocedural pain.

RESULTS A total of 209 patients who underwent 679 procedures were included in this study. The mean age at first intervention was 11.8 ± 4.5 years. Inadequately controlled postprocedural pain was found in 34.8% of the 679 procedures. Venous malformations (VM) were the most prevalent subtype of vascular malformation (80%), followed by arteriovenous malformations (AVM) (14.6%) and lymphatic malformations (LM) (5.4%). The odds ratio (OR) (95% confidence intervals), and *P* values obtained from multivariable mixed effect logistic regression analysis for patient and treatment characteristics found to be associated with inadequately controlled postprocedural pain were: chronic use of analgesics (OR 2.74 (1.40 to 5.34), $P = 0.003$), treatment with ethanol (OR 2.39 (1.01 to 5.65, $P = 0.05$) or esketamine (OR 7.43 (1.32 to 41.81), $P = 0.02$). Patients treated with lauromacrogol (OR 0.42 (0.22 to 0.82, $P = 0.01$) and patients receiving intra-operative NSAIDs (OR 0.32, (0.12 to 0.85), $P = 0.02$) were less likely to experience inadequately controlled postprocedural pain.

CONCLUSIONS Despite aiming to achieve best practice, the 34.8% incidence of unsatisfactory postoperative pain management in the children studied confirms that postprocedural pain after sclerotherapy is a common problem that requires further attention.

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KEY POINTS

- There is no information in the scientific literature about the incidence and extent of pain related to sclerotherapy of vascular malformations in children.
- Despite aiming for best possible practice, in more than a third of the interventions there was a lack of satisfactory postoperative analgesia.
- This is the first step towards setting prospective interventional studies and clinical guidelines to improve the peri-operative pain experience in these children.

INTRODUCTION

Vascular malformations are lesions localised to blood or lymph vessels and they encompass a broad spectrum of pathologies.[1–8] Depending on the subtype, size and location, these malformations can cause a variety of symptoms ranging from mild symptoms such as skin discoloration and swelling to more severe manifestations including pain, ulceration, bleeding, necrosis, disfigurement and cardiac failure. Although patients can remain asymptomatic, such vascular malformations can potentially proliferate over time due to hormonal changes (e.g., during puberty, pregnancy or as an effect of hormone therapy), causing sudden rapid expansion of the lesion.[1–4] In order to treat symptoms, curtail disease progression, or prevent serious complications most subtypes of vascular malformations require medical or surgical intervention.[1,2]

Current treatment modalities include sclerotherapy, cryoablation, laser photocoagulation, surgical resection and medical management involving systemic therapy. Injection of a sclerosing agent is the most common treatment modality for most vascular malformations, but often requires multiple interventions.[2,4,9–13] Ethanol is one of the most potent and frequently used sclerosing agent, but it also presents the highest risk of developing complications.[14–16] Postprocedural pain is frequently mentioned as one of the various possible complications of sclerotherapy, along with bleeding, infection, and skin necrosis.[2,7,13,17,18] Although inadequately controlled postprocedural pain in this group is a common and widely recognised problem among clinicians, little to no quantifiable data is available.[11,13,18,19]

Gaining new insights into the extent of postprocedural pain after sclerotherapy, and its risk factors, is an important first step towards improving its management in patients with vascular malformations, and eventually implementing a uniform evidence-based protocol on postprocedural pain management. The primary objective of this study is to quantify the incidence of postprocedural pain in this paediatric group. Secondary objectives were to identify risk factors for such pain based on patient-, treatment-, and medication-related characteristics.

METHODS

Formal ethical approval for this study (2020-6471) was obtained on 27 May 2020 from the Central Committee on Research Involving Human Subjects (CMO) Radboudumc, Geert Groteplein zuid 10a, Nijmegen, The Netherlands. Request for informed consent was wavered.

Data source and study population

The data used in this retrospective longitudinal single-centre study was extracted from the electronic patient records (EPD) of patients treated by the centre of expertise for haemangiomas and congenital vascular malformations Nijmegen (HECOVAN) at the Radboud University Medical Centre (Radboudumc), The Netherlands. Radboudumc sees an average of more than 600 new referrals of adults and children per year. It is one of the busiest centres within the corresponding European reference network. Between October 2013 and July 2020, 1037 patients underwent sclerotherapy procedures: 291 were 16 years of age or younger when they underwent the first intervention. All included patients from 0 to 16 years at the time of the first procedure were treated at Radboudumc. Follow-up procedures were included without age restrictions. We have adhered to the classification and nomenclature used by the International Society for the Study of Vascular Anomalies (ISSVA) in the 2018 Classification system.[20,21] We included patients with only 'simple' subtypes of vascular malformations, which include capillary malformations (CM), lymphatic malformations (LM), venous malformations (VM), arteriovenous malformations (AVM), and arteriovenous fistula (AVF). Through manual screening of the electronic patient records patients were excluded for the following reasons: primarily treated in an other hospital, no procedure, not a vascular malformation or simple subtype malformation, received alternative treatment option before sclerotherapy, opted out of the use of medical records for research purposes, intracranial vascular malformation, incomplete medical records and genetic disorder associated with vascular malformation. Patients with genetic disorders were excluded to establish a more homogenous and comparable study population.

The sclerosing agents used for sclerotherapy at Radboudumc were bleomycin, lauromacrogol and ethanol, which were either used as monotherapy or in combination with other sclerosants. The dose of bleomycin (Bleomedac, Lamepro BV, Breda, Netherlands) was 600 IU kg^{-1} with a maximum of 10 000 IU per session. Lauromacrogol (Aethoxysklerol, Chemical Factory Kreussler & Co., Wiesbaden, Germany) was used with a concentration of 2% or 3% as foam (2 ml lauromacrogol with 8 ml sterile

room air) with a maximum of 30 ml of foam per session. Ethanol (alcohol 96%, Pharmacy A15, Gorinchem, Netherlands) with a maximum of 0.14 ml kg^{-1} body weight per 10 min was used and a maximum of 0.5 to 1.0 ml kg^{-1} per session.

Variables such as age and sex and most treatment-related variables were automatically extracted from the EPD. However, observational variables such as postprocedural pain and complications and missing data had to be manually reviewed and recorded in the database. Any adverse events (drug-related, procedure-related, wound-related or anaesthesiology-related) were recorded manually. Ethanol especially has been associated with rare complications, notably pulmonary hypertension and acute pulmonary oedema.[22]

Postprocedural pain experienced by the patient is frequently monitored until discharge from the recovery unit to the ward and before discharge home. This is registered in the EPD using a Numeric Rating Scale (NRS) and Visual Analog Scale (VAS) as validated pain assessment tools. Missing EPD pain scores were complemented by nurses' clinical observation and descriptive postprocedural pain assessments documented in the EPD. Inadequate postprocedural pain management was defined as a pain score of $\geq$4, in accordance with the European Society for Paediatric Anaesthesiology (ESPA) Guidelines.[23] Patients were mainly treated on a day case basis. Morphine (10 to 20 ug kg^{-1} $dose^{-1}$), paracetamol (maximum of 90 mg kg^{-1} day^{-1}) and diclofenac(1 to 3 mg kg^{-1} day^{-1}) were the standard postoperative pain protocol.

The primary outcome of this study was to quantify postprocedural pain. Secondary outcome measures were patient characteristics, treatment characteristics, types of periprocedural (pre-operative, intra-operative and post-operative) analgesics administered and the potential correlation between inadequately controlled postprocedural pain (as dependent variable) and patient characteristics and treatment characteristics.

STATISTICAL ANALYSIS

Descriptive statistics were used to describe the primary outcome. Candidate predictor variables were determined based on clinical relevance and data spread. The anaesthetic technique and postprocedural outcome variables, except for postprocedural pain, were excluded from analysis (e.g., hospital stay). Because the longitudinal repeated measures design of this study (patients undergoing multiple procedures) does not meet the assumption of independence of observations that is required for a normal logistic regression analysis, a multilevel logistic regression model with a random intercept per patient was chosen for the statistical analysis. This model corrected for the fact that some patients underwent multiple interventions. The pseudo-anonymised patient ID was assigned as a random effect variable in order to account for within-subject correlation between repeated measurements. Postprocedural pain was assigned as a binary dependent outcome variable and independent variables were categorised into patient characteristics, treatment characteristics and medication characteristics. Variables were analysed using univariate analysis with the exception of variables with levels that were dummy coded independently due to multiple possible combinations of options (e.g., types of sclerosant and types of analgesics). These were modelled in a multivariable analysis to adjust for each variable level. Variables that contained almost no data or were present in almost all interventions were combined into new variables for univariate analysis. The outcome of this analysis was expressed in odds ratios (OR) with a 95% confidence interval (95% CI). A two-tailed *P*-value of $\leq$0.05 was considered as statistically significant. After univariate variable analyses categorical variables that were significant in the univariable analysis with a $P \leq 0.05$ were entered into a multivariable analysis with inadequate postprocedural pain as the dependent variable.

List-wise deletion was performed to handle missing data, all interventions with missing data in one of the variables analysed were excluded from the dataset.

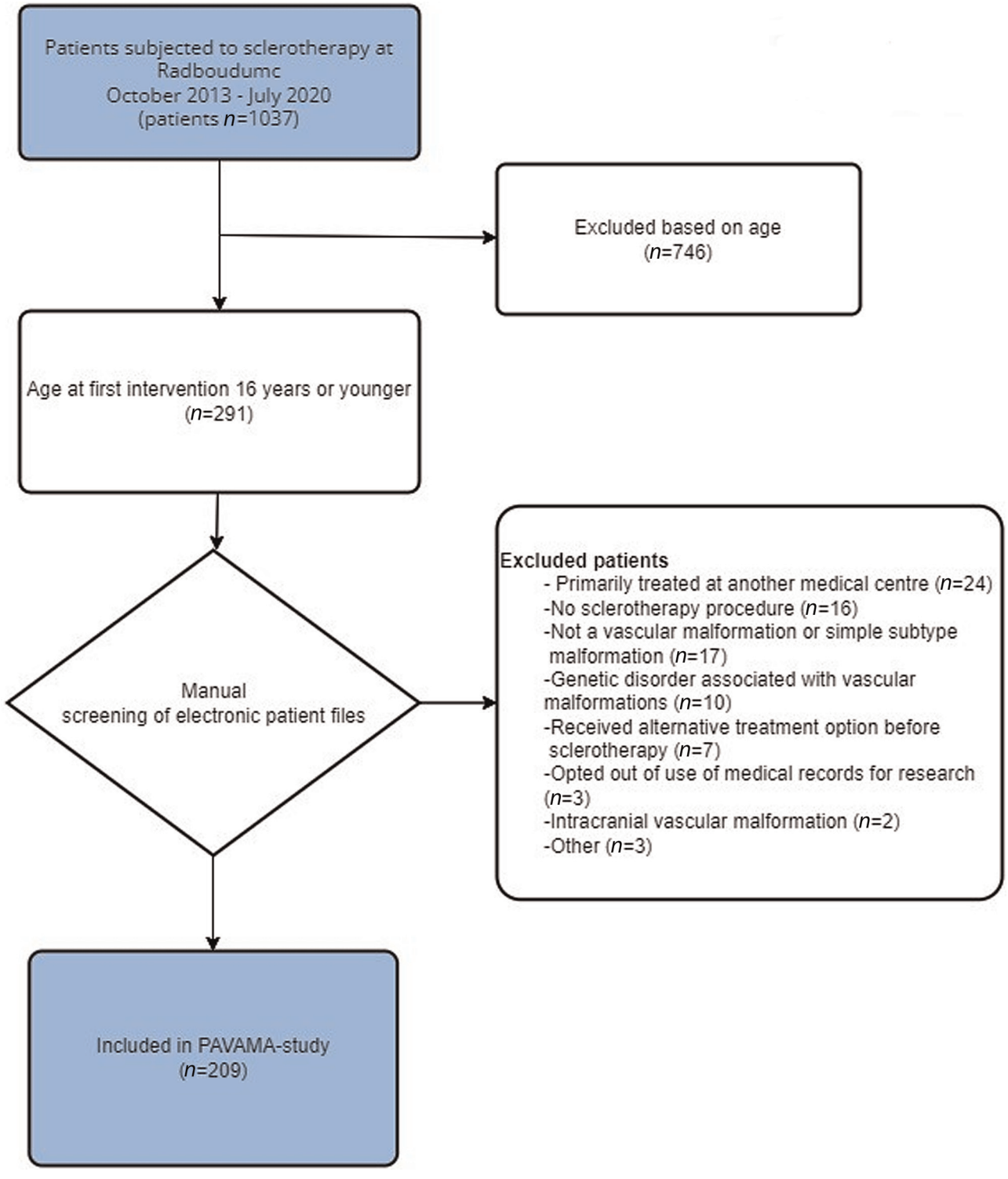
The data was tested for skewness, kurtosis, normal distribution and was centred accordingly. Collinearity was tested by calculating the Generalized Variance Inflation Factor (GVIF) with a threshold of >10 and cross-checked using Pearson's correlation test with scatter plots where appropriate. With the exception of influential values because the data was not tested for possible outliers, the assumptions for logistic regression were adequately met. Statistical analyses were performed using RStudio software packages (version 4.0.3).

RESULTS

A total of 291 patients, 16 years or younger, were selected, of which 82 were excluded leaving 209. A flowchart illustrating the patient selection is shown in Fig. 1. Many of the included patients (150) received multiple sessions of sclerotherapy, with a total of 679 interventions included in this study: a median [IQR] of 2 [1 to 4] sessions per patient.

Table 1 shows the baseline patient-, lesion- and treatment-related characteristics of all interventions included in this study. Out of the 679 interventions, 34.8% had inadequately controlled pain in the postoperative period (recovery and ward). Of the 209 patients, 112 (53.6%) experienced inadequately controlled pain at least once after an intervention. The mean age of the total study cohort was 11.8 $\pm$ 4.5 years and was comparable in both groups. Overall, 62.9% of the patients were female and 37.1% male. The VMs had the highest prevalence (80%), followed by AVMs (14.6%) and LMs (5.4%). AVFs and CMs were not present in this study sample. Vascular

FIGURE 1 Flow chart.



malformations were most frequently located in the lower extremities (48.2%), followed by the craniofacial region (27.0%) and the upper extremities (14.7%). The most common treatment indication in this group was pain (69.4%), followed by cosmetic reasons (15.3%). Malformation subtypes, lesion localisations and treatment indications are proportionately represented in the different subset of patients.

Table 1 Characteristics per intervention of patients with and without adequately controlled pain. Data are presented mean ± SD [range], number (%)

	Total interventions $n = 679$	Adequately controlled pain (pain score < 4) $n = 443$	Inadequately controlled pain (pain score ≥ 4) $n = 236$
Patient characteristics			
Sex			
Male	252 (37.1)	174 (39.3)	78 (33.1)
Female	427 (62.9)	269 (60.7)	158 (66.9)
AGE, years			
Mean ± SD [range]	11.8 ± 4.5 [0 to 21]	11.3 ± 4.8 [0 to 21]	12.6 ± 3.8 [2 to 20]
ASA-classification			
ASA I	610 (89.8)	394 (88.9)	216 (91.5)
ASA II	68 (10.0)	48 (10.8)	20 (8.5)
ASA III	1 (0.1)	1 (0.2)	0 (0.0)
Comorbidity			
None	621 (91.6)	407 (91.9)	214 (91.1)
Yes	57 (8.4)	36 (8.1)	21 (8.9)
Missing data	1 (0.1)	0 (0.0)	1 (0.4)
Malformation and intervention characteristics			
Subtype			
Venous malformation (VM)	543 (80.0)	337 (76.1)	206 (87.3)
Arteriovenous malformation (AVM)	99 (14.6)	76 (17.2)	23 (9.7)
Lymphatic malformation (LM)	37 (5.4)	30 (6.8)	7 (3.0)
Location lesion			
Lower extremities	327 (48.2)	207 (46.7)	120 (50.8)
Craniofacial	183 (27.0)	134 (30.2)	49 (20.8)
Upper extremities	100 (14.7)	56 (12.6)	44 (18.6)
Torso	29 (4.3)	22 (5.0)	7 (3.0)
Genitalia	27 (4.0)	13 (2.9)	14 (5.9)
Abdomen	9 (1.3)	8 (1.8)	1 (0.4)
Oropharynx	4 (0.6)	3 (0.7)	1 (0.4)
Duration intervention, minutes			
Mean ± SD [range]	48.0 ± 31.9 [13 to 641]	49.0 ± 36.9 [15 to 641]	46.3 ± 19.8 [13 to 170]
Missing data	6 (0.9)	6 (1.4)	0 (0.0)
Treatment indication			
Pain	441 (69.4)	267 (64.3)	174 (79.1)
Cosmetic	97 (15.3)	67 (16.1)	30 (13.6)
Asymptomatic	46 (7.2)	46 (11.1)	0 (0.0)
Complications	15 (2.2)	11 (2.5)	4 (1.7)
Other reason	36 (5.7)	24 (5.8)	12 (5.5)
Unknown	44 (6.5)	28 (6.3)	16 (6.8)
Type of sclerosing agent			
Ethanol	538 (79.2)	329 (74.3)	209 (88.6)
Bleomycin	29 (4.3)	26 (5.9)	3 (1.3)
Lauromacrogol (Aethoxysklerol)	232 (34.2)	176 (39.7)	56 (23.7)
Combination sclerosing agents Ethanol + Bleomycin	120 (17.7)	88 (19.9)	32 (13.6)
Ethanol + Lauromacrogol	3 (0.4)	3 (0.7)	0 (0.0)
Bleomycin + Lauromacrogol	109 (16.1)	79 (17.8)	30 (12.7)
Ethanol + Bleomycin + Lauromacrogol	8 (1.2)	7 (1.6)	1 (0.4)
	0 (0.0)	0 (0.0)	0 (0.0)
Anaesthesiology characteristics			
Anaesthetic technique [a]			
General anaesthesia	669 (98.5)	435 (98.2)	234 (99.2)
Combined Inhalation + Intravenous anaesthesia	510 (75.1)	326 (73.6)	184 (78.0)
Inhalation anaesthesia	146 (21.5)	106 (23.9)	40 (16.9)
Total intravenous anaesthesia (TIVA)	22 (3.2)	10 (2.3)	12 (5.1)
Pre-operative regional anaesthesia	10 (1.5)	1 (0.2)	0 (0.0)
Nerve/plexus block	8 (1.2)	6 (1.4)	2 (0.8)
Subcutaneous infiltration	2 (0.3)	2 (0.5)	0 (0.0)
Combined general + regional anaesthesia	9 (1.3)	7 (1.6)	2 (0.8)

[a] Combinations of variable options are not documented in this table.

The use of the sclerosing agents and combinations are shown in Table 1. At 79.2% of interventions, ethanol was the most frequently used. All but one patient received general anaesthesia, and 9 (1.3%) of these also received a nerve/plexus block or local subcutaneous infiltration. Table 2 presents the total amount of peri-procedural medication administration during various phases of the procedure. Patients may have received a

combination of several types of medication, but only the aggregated total of each drug is documented in this table. In 20.5% of cases, analgesics were used at home with 61.2% of this group using it for a prolonged period of ≥6 weeks. For patients undergoing treatment because of pain, 26.5% used analgesics at home. The most frequently used type of home analgesic were NSAIDs (82.7%) and paracetamol (64%). Analgesics were administered before the procedure in 64.3% of all cases. Of the 431 procedures where analgesic premedication was provided, paracetamol was the drug of choice (99.5%). Local anaesthetic EMLA cream was applied in 23.9% of procedures to facilitate intravenous cannulation.

Table 2 **Analgesics used peri-operatively**

	Total interventions *n* = 679	Adequately controlled pain (pain score < 4) *n* = 443	Inadequately controlled pain (pain score ≥ 4) *n* = 236
Home medication			
Home use of analgesics			
None	540 (79.5)	373 (84.2)	167 (70.8)
Yes	139 (20.5)	70 (15.8)	69 (29.2)
Nonchronic use <6 weeks	54 (8.0)	33 (7.4)	21 (8.9)
Chronic use ≥6 weeks	85 (12.5)	37 (8.4)	48 (20.3)
Type of home use analgesic [a]			
Paracetamol	89 (13.1)	42 (9.5)	47 (19.9)
NSAID	115 (16.9)	57 (12.9)	58 (24.6)
Opioids	34 (5.0)	15 (3.4)	19 (8.1)
Other	4 (0.6)	1 (0.2)	3 (1.3)
NSAID + paracetamol	65 (9.6)	29 (6.5)	36 (15.3)
NSAID + paracetamol + opioids	23 (3.4)	14 (3.2)	9 (3.8)
Pre-procedural medication			
administration of pre-procedural medication			
None	148 (21.8)	100 (22.6)	48 (20.3)
Yes [a]	522 (76.9)	340 (76.7)	182 (77.1)
Analgesics	431 (63.5)	278 (62.8)	153 (64.8)
EMLA-cream	160 (23.6)	101 (22.8)	59 (25.0)
Midazolam	260 (38.3)	163 (36.8)	97 (41.1)
Other	4 (0.6)	3 (0.7)	1 (0.4)
Missing data	9 (1.3)	3 (0.7)	6 (2.5)
Type of analgesic [a]			
Paracetamol	429 (63.2)	277 (62.5)	152 (64.4)
NSAID	1 (0.1)	0 (0.0)	1 (0.4)
Opioid	0 (0.0)	0 (0.0)	0 (0.0)
Other analgesic	2 (0.3)	1 (0.2)	1 (0.4)
Missing data	9 (1.3)	3 (0.7)	6 (2.5)
Intra-procedural medication			
Administration of intra-procedural medication			
Analgesics	678 (99.9)	442 (99.8)	236 (100.0)
Corticosteroids	632 (93.1)	403 (91.0)	229 (97.0)
Midazolam	24 (3.5)	15 (3.4)	9 (3.8)
Type of analgesic [a]			
Paracetamol	96 (14.1)	74 (16.7)	22 (9.3)
NSAID	646 (95.1)	426 (96.2)	220 (93.2)
Opioids	670 (98.7)	438 (98.9)	232 (98.3)
Metamizole	116 (17.1)	76 (17.2)	40 (16.9)
Clonidine	56 (8.2)	42 (9.5)	14 (5.9)
Esketamine	11 (1.6)	3 (0.7)	8 (3.4)
Nerve/plexus block	4 (0.6)	3 (0.7)	1 (0.4)
Post-procedural medication			
Administration of post procedural medication			
Midazolam	2 (0.3)	0 (0.0)	2 (0.8)
Analgesics	317 (46.7)	112 (25.3)	205 (86.9)
Type of analgesic			
Paracetamol	202 (29.7)	98 (22.1)	104 (44.1)
NSAID	82 (12.1)	23 (5.2)	59 (25.0)
Opioids	193 (28.4)	22 (5.0)	171 (72.5)
Metamizole	5 (0.7)	0 (0.0)	5 (2.1)
Clonidine	19 (2.8)	1 (0.2)	18 (7.6)
Esketamine	5 (0.7)	0 (0.0)	5 (2.1)
Nerve/plexus block	4 (0.6)	1 (0.2)	3 (1.3)

Data are presented as number (%). [a]Combinations of variable options are not documented in this table.

During all except one intervention (which was under regional anaesthesia only), all patients received analgesics intra-operatively. Opioids and NSAID were administered in 98.7% and 95.1% of the cases respectively. Corticosteroids (intravenous prednisolone 1.5 mg kg^{-1} body weight to a maximum of 100 mg) intra-operatively were provided in 93% of interventions. In 46.7% of interventions patients received additional analgesics during the postprocedural phase in the recovery room or ward, of which 64.7% developed inadequately controlled postprocedural pain at some point after the procedure. Paracetamol was the most frequently administered type of analgesic during the postprocedural phase (63.7% of postprocedural analgesic administration), followed by opioids (60.9% of postprocedural analgesic administration).

Table 3 shows the outcome after the sclerotherapy procedure. The average hospital stay was 1.1 ± 0.6 days. In 94.6% of the cases, patients were discharged on the day of the procedure. One patient was hospitalised for 11 days after the procedure. Only 0.7% were re-admitted <31 days after discharge. The most frequent adverse event was postoperative nausea and vomiting. We did not observe any ethanol specific complications (pulmonary oedema or pulmonary hypertension)[22] in our study cohort.

Univariate and multivariable mixed effects logistic regression analysis

Table 4 shows the results of the univariate mixed effects logistic regression analysis with inadequate postprocedural pain as the dependent variable. Variables ''premedication other'' and ''premedication NSAID were combined into ''premedication other'' variable. The variable, ''intra-operative regional block'', was removed from univariate analysis because it was used in only 4 patients. An increase in age by one year was significantly associated with inadequately controlled postprocedural pain after sclerotherapy, with a OR (95% CI) of 1.09 (1.03 to 1.16). Chronic use of analgesics for a period >6 weeks was associated with inadequate postprocedural pain with an OR of 2.69 (1.43 to 5.06). Patients with inadequately controlled postprocedural pain were most frequently treated with ethanol during the procedure. Esketamine was administered intra-operatively during 11 procedures, this was an individual choice of the anaesthesiologist and was not related to a specific patient or a clinical context. Patients who received esketamine had a higher odds of developing postprocedural pain during univariate analysis. In 93.1% of the interventions corticosteroids were administered intra-operatively. In univariate analysis, administration of corticosteroids gave an OR of 5.05 (1.82 to 14.03) for developing inadequately controlled postprocedural pain. Patients with venous malformations had a significantly increased OR of 4.67 (1.26 to 17.37) for developing inadequate postprocedural pain

Categorical variables with a $P \leq 0.05$ in the univariate analysis were included in the multivariable model. The results of multivariable mixed effects logistic regression analysis are displayed in Table 4. Chronic use of analgesics [OR 2.74 (1.40 to 5.34)), intra-operative administration of esketamine (OR 7.43 (1.32 to 41.81)] and ethanol as sclerosant (OR 2.39 (1.01 to 4.65)) were associated with increased postoperative pain after multivariable mixed effects logistic regression analysis. Patients receiving intra-operative NSAIDs, or who were treated with lauromacrogol were less likely to develop postprocedural pain: OR 0.32 (0.12 to 0.85) and 0.42 (0.22 to 0.82), respectively.

DISCUSSION

This single-centre retrospective cohort study of 209 patients with vascular malformations indicates an incidence of

Table 3 Outcome characteristics for the 679 interventions. Data are mean ± SD [range], or number (%)

	Total interventions $n = 679$	Adequately controlled pain (pain score < 4) $n = 443$	Inadequately controlled pain (pain score ≥4) $n = 236$
Hospital stay (days)	1.1 ± 0.6 [1 to 11]	1.0 ± 0.2 [1 to 2]	1.2 ± 0.9 [1 to 11]
1 day	642 (94.6)	435 (98.2)	207 (87.7)
≥ 2 days	37 (5.4)	8 (1.8)	29 (12.3)
Adverse events			
None	633 (93.2)	429 (96.8)	204 (86.4)
Yes	46 (6.8)	14 (3.2)	32 (13.6)
Drug-related	2 (0.3)	0 (0.0)	2 (0.8)
Procedure-related	13 (1.9)	3 (0.7)	10 (4.2)
Wound-related	1 (0.1)	0 (0.0)	1 (0.4)
Anaesthesiology related	23 (3.4)	9 (2.0)	14 (5.9)
Other adverse outcome	9 (1.3)	2 (0.5)	7 (3.0)
Combination	2 (0.3)	0 (0.0)	2 (0.8)
Readmittance <31 days after discharge			
No	674 (99.3)	443 (100)	231 (97.9)
Yes	5 (0.7)	0 (0.0)	5 (2.1)

Table 4 Results of univariate and multivariable mixed effects logistic regression analysis for predicting an association with inadequately controlled pain

Variables	Univariate OR	*P*-value	Mutivariable OR	*P*-value
Age (increase per year)	1.09 (1.03 to 1.16)	<0.004	1.05 (0.97 to 1.12)	0.23
Sex (female)	1.65 (0.93 to 3.06)	<0.091	–	–
ASA classification (ASA I reference)				
ASA II/III	0.66 (0.31 to 1.38)	0.27	–	–
Comorbidity present	0.81 (0.31 to 1.98)	0.64	–	–
Subtype lesion (lymphatic reference)				
Arteriovenous malformation	2.19 (0.49 to 9.65)	0.299	0.33 (0.05 to 2.19)	0.25
Venous malformation	4.67 (1.26 to 17.37)	0.021	1.08 (0.19 to 6.29)	0.93
Location lesion (craniofacial reference)				
Oropharynx	0.99 (0.05 to 22.02)	0.99	–	–
Upper extremities	2.88 (1.25 to 6.65)	0.01	–	–
Torso	0.77 (0.20 to 2.99)	00.70	–	–
Abdomen	0.35 (0.02 to 5.32)	0.45	–	–
Genitalia	2.59 (0.39 to 17.3)	0.33	–	–
Lower extremities	1.96 (0.99 to 3.85)	0.05	–	–
Treatment indication (other reference)				
Cosmetic reasons	1.04 (0.33 to 3.24)	0.95	1.27 (0.35 to 4.71)	0.72
Complications	0.73 (0.15 to 3.68)	0.70	0.83 (0.14 to 4.88)	0.83
Asymptomatic	0.000 (0 to ∞)	0.99	0.00 (0.00 to infinite)	0.94
Pain	1.42 (0.55 to 3.67)	0.47	0.84 (0.27 to 2.61)	0.77
Type of sclerosant [b]				
Ethanol	2.37 (1.11 to 5.27)	0.03	2.39 (1.01 to 5.65)	0.05
Bleomycin	0.29 (0.05 to 1.34)	0.14	0.85 (0.09 to 7.66)	0.88
Lauromacrogol	0.50 (0.28 to 0.90)	0.02	0.42 (0.22 to 0.82)	0.01
Home use of analgesics (none reference)				
Chronic use ≥6 weeks	2.69 (1.43 to 5.06)	0.002	2.74 (1.40 to 5.34)	0.003
Nontochronic use <6 weeks	0.99 (0.46 to 2.15)	0.98	0.93 (0.40 to 2.16)	0.87
Type of home use analgesics [b]				
Paracetamol	1.68 (0.81 to 3.47)	0.16	–	–
NSAID	1.15 (0.55 to 2.39)	0.70	–	–
Opioid	1.36 (0.49 to 3.82)	0.55	–	–
Other	3.95 (0.25 to 159.13)	0.38	–	–
Administration of pretomedication	1.14 (0.71 to 1.86)	0.59	–	–
Type of pretomedication[b]				
Paracetamol	0.47 (0.01 to 15.91)	0.65	–	–
Other	0.40 (0.01 to 5.95)	0.53	–	–
Midazolam	1.33 (0.86 to 2.07)	0.21	–	–
Types of intra-operative Analgesics[b]				
Paracetamol	0.50 (0.26 to 0.95)	0.04	0.79 (0.40 to 1.53)	0.48
NSAID	0.37 (0.15 to 0.94)	0.04	0.32 (0.12 to 0.85)	0.02
Opioid	0.34 (0.06 to 1.98)	0.23	0.29 (0.05 to 1.66)	0.16
Metamizole	0.91 (0.53 to 1.58)	0.74	0.76 (0.42 to 1.38)	0.37
Clonidine	0.53 (0.24 to 1.17)	0.11	0.46 (0.19 to 1.09)	0.08
Esketamine	9.47 (1.75 to 51.18)	0.009	7.43 (1.32 to 41.81)	0.02
Administration of corticosteroids	5.05 (1.82 to 14.03)	0.002	2.75 (0.91 to 8.30)	0.07

Data are presented as odds ratio (95% confidence interval). NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio. [a]OR per unit increase of variable. [b] Corrected multivariable mixed model logistic regression using dummy coded variables mentioned.

inadequately controlled postprocedural pain of 34.8% from over a total of 679 sclerotherapy procedures.

Previous studies have shown that existence of chronic pain is a risk factor for severe postoperative pain.[24] Chronic pain before treatment was not registered in this study. However, we did register chronic use of analgesics for longer than 6 weeks. This was associated with an increase of postprocedural pain after both univariate and multivariable analysis. Patients who used analgesics for longer than 6 weeks were likely to suffer from chronic pain. Therefore, this finding indicates that the existence of chronic pain is an important risk factor for inadequate postprocedural pain in patients undergoing sclerotherapy treatment for vascular malformations.

Of the three sclerosant agents, a significant association with inadequately controlled postprocedural pain was found for ethanol [OR 2.39 (1.01 to 4.65)] after both univariate and multivariable analysis. Compared with the others, ethanol is one of the most effective sclerosing agents but also the most aggressive, with the highest complication rate (including severe swelling and pain) of up 61%.[14,16] The use of the less aggressive lauromacrogol was associated with decreased odds [0.42 (0.22 to 0.82)] of developing inadequately controlled postprocedural pain. These findings should be kept in mind by clinicians looking after these patients and they

should plan perioperative pain management according to the sclerosing agent to be used.

The intra-operative administration of NSAID's was associated with decreased odds of developing inadequately controlled postprocedural pain. Given the clinical implications, this finding should be investigated prospectively in future studies.

Studies on the postprocedural analgesic effect of corticosteroids are limited. However, two large meta-analyses have found a significant reduction in pain score and opioid consumption after periprocedural intravenous corticosteroid administration.[25,26] Our results were conflicting. In 93% of the interventions intra-operative corticosteroids were administered, and we noted a significantly increased univariate odds of developing inadequately controlled postprocedural pain in these patients. However, this finding was not evident in the multivariable analyses Therefore, it remains a challenge as to how our findings should be interpreted.

In our study, intra-operative administration of esketamine was associated with an increased OR of developing inadequately controlled postprocedural pain [7.43 (1.32 to 41.81), $P < 0.02$], despite the analgesic properties of ketamine. We do not have an explanation for such a finding and given the limited number of patients ($n = 11$) it would be inappropriate to draw definitive conclusions.

Age was associated with inadequately controlled pain after univariate analysis with an increase of 9% per year of age. However, after multivariable analysis, age was no longer a significant factor with an odds-ratio P-value of 0.23. Vascular malformations proliferate due to hormonal changes, for example, during puberty, and venous malformations may even progress more than twice as frequently in adolescents as in children according to one study.[27,28] Therefore, these findings suggest that as the size of vascular malformation increases with age, this is associated with a need for more extensive treatment and inadequately controlled postprocedural pain.

There are several limitations of this study that need to be addressed. First, because this study was based on retrospective data, it is uncertain at which point during the postprocedural phase the pain score and analgesic administration had been recorded, however there is a prevailing tendency within our institution to minimise the unnecessary use of opioids in children. Consequently, the administration of postoperative analgesics is only performed after an assessment of pain by the attending nurses.

Second, a baseline pain score before the intervention was not documented, which makes interpreting the postprocedural pain scores more challenging. Pain assessments at specific times (e.g., 1 h before, and 30 and 90 min after the procedure) would counteract this problem in future prospective research and would improve the consistency and validity of data. Evaluation of pain scores at one week and one month postoperatively would also be informative to help to adjust the analgesic strategy. Unfortunately, these data were not available for this study. In order to compare the effectiveness of different types of analgesics, changes from a baseline pain score after administration of postprocedural analgesics should be considered as an additional outcome variable in future studies. The Pain Management Index (PMI) could be a useful tool for this objective, as its scoring system is based on the NRS and the type of analgesic administered.[29]

A third limitation is that the type of opioids administered peri-operatively was not registered in our dataset.

Fourth, the outcome variable was expressed as a binary variable. Categorisation of patients into the two groups with adequately and inadequately controlled postprocedural pain was primarily based on the postprocedural pain score threshold of ≥ 4 on the NRS/VAS. This dichotomisation of continuous data is common practice in clinical research, but could be problematic due to loss of information and can lead to a reduction of power.[30] Due to incomplete registration of pain scores in the EPD, pain scores and clinical assessment documented in the nursing notes were also taken into account for the classification of postprocedural pain. Patients were discharged to the referring hospital with no further access to short- or long-term postoperative data. The use of unvalidated subjective measures may have introduced an observer and misclassification bias.[31]

Finally, a shortcoming of single-centre studies is the limited external validity and generalisability of the data.[32]

Clinical implications

To our knowledge, this is the first study with a sizeable study cohort that has quantified inadequately controlled postprocedural pain and evaluated predictive factors in patients with vascular malformations. The 34.8% incidence confirms that postprocedural pain after sclerotherapy is a common problem that requires improvements in pain management.

Short-term consequences of inadequately managed acute postprocedural pain are delayed discharge and a prolonged duration of. However, persisting postprocedural pain can manifest as chronic postsurgical pain (CPSP), resulting in a lower quality of life, increased morbidity and psychological distress.[33] Postprocedural pain can also cause prolonged behavioural changes in children for up to 4 weeks, even after the initial pain has subsided.[34]

Based on the incidence of postprocedural pain in this study we suggest that regional anaesthesia should be considered when feasible. Furthermore, the use of long-acting opioids should be considered more often. Despite the trend for day-case treatment, anaesthesiologists should not be dissuaded from using longer-acting

opioids intra-operatively. Furthermore, our research outcome supports the more frequent use of peri-operative NSAID.

Analysing epidemiological data and identifying potential risk factors for postprocedural pain in this patient group was a fundamental first step for improving peri-operative pain management. To ascertain the effectiveness of different analgesic strategies, future studies will require the co-operation and collaboration with other centres providing similar care to this group.

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