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ABSTRACT

BACKGROUND AND PURPOSE: Fibrin glue is increasingly incorporated as a component in epidural blood patching (EBP) for the treatment of spinal CSF leaks. Hypersensitivity reactions are a potential complication of its use but are not well studied in the setting of EBP. The purpose of this study was to determine the incidence of hypersensitivity reactions to fibrin glue during EBP and to identify any predisposing factors associated with increased patient risk.

MATERIALS AND METHODS: A single-center retrospective cohort study with nested case-control design included patients who received fibrin glue EBP for the treatment of iatrogenic CSF leaks or spontaneous intracranial hypotension over 13 years. Patient demographics and multiple procedure-specific variables were collected. Cases were identified from the total cohort as those with hypersensitive reactions and matched with controls in a 1:3 ratio. The incidence of hypersensitivity reactions in the total cohort was calculated. Logistic regression models were fit to test for associations between variables and the development of a hypersensitivity reaction.

RESULTS: A total of 3065 CT-guided EBPs with fibrin glue were identified in 1574 individual patients. The incidence of hypersensitivity reactions was 0.49% per procedure and 0.95% per patient and never occurred during the first EBP with fibrin glue. Case-control analysis found higher odds for hypersensitivity reactions in patients with a lower BMI (OR 0.82 [0.71–0.96], $P = .003$), younger age (OR 0.95 [0.91–0.99], $P = .011$), and during procedures with inadvertent intravenous injections (OR 5.44 [1.34–22.01], $P = .014$).

CONCLUSIONS: We found a 0.49% incidence of hypersensitivity reactions during EBP with fibrin glue, none occurring during the first exposure. Younger age, lower BMI, and inadvertent intravenous injection during the procedure were associated with a higher likelihood of reactions. This study provides data useful for counseling patients on procedural risk and identifies variables for physicians to be aware of to help prevent life-threatening reactions to fibrin glue during EBP.

ABBREVIATIONS: CVF = CSF-venous fistula; EBP = epidural blood patching; SIH = spontaneous intracranial hypotension

Spontaneous intracranial hypotension (SIH) is an incapacitating condition caused by spinal CSF leaks. It causes headaches and cranial nerve-related symptoms, significantly affecting a patient's quality of life.[1,2] SIH is underdiagnosed, particularly given the variable presentation and somewhat nonspecific symptoms coupled with often subtle imaging findings, and it is, therefore, likely more prevalent than currently recognized.[3,4] The most common method of treatment for SIH is epidural blood patching (EBP), which involves the percutaneous placement of blood and/or fibrin glue into the epidural space to seal the dural defect.[5] While EBP is generally considered a safe procedure with low adverse event rates, one notable potential complication is an allergic reaction to patching material when including fibrin glue.[6] Recent publications have advocated for the use of fibrin glue in EBP, purporting increased efficacy.[7] Therefore, understanding the risk profile of EBP with fibrin glue is of particular importance, given the known potential for anaphylaxis in some patients.[6]

Historically, a variety of materials have been used in epidural patching, ranging from catgut, gelatin, and saline, eventually arriving at blood, which was established as the treatment standard by Dr. Gormley in 1960.[8] Autologous blood continues to be the primary patching material in most EBP procedures. More recently, fibrin glue, which was introduced as a patching material in 1985,

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From the Departments of Radiology (J.L.S., M.J.K., L.G., M.D.M., P.G.K., T.J.A.), and Department of Pediatrics (A.P.S.), Allergy and Immunology, Duke University Medical Center, Durham, North Carolina and Department of Biostatistics and Bioinformatics (S.M., A.E.), Duke University School of Medicine, Durham, North Carolina.

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Please address correspondence to Timothy J. Amrhein, MD, Department of Radiology, Box 3808, Duke University Medical Center, Durham, NC, 27710; e-mail: timothy.amrhein@duke.edu

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when it was first used to repair iatrogenic dural tears, has become increasingly utilized, particularly at referral centers.[9,10] Fibrin glue is a sealant that is utilized often in the setting of surgery and has been shown to successfully repair dural tears with few complications, which makes it an attractive ingredient for epidural patching.[11] A key component of fibrin glue is aprotinin, which carries with it an increased risk of hypersensitivity reactions. The rates and risks of reactions to fibrin glue in surgery have been well documented and range from <0.1% to 1.8%.[12] However, the incidence of hypersensitivity reactions during epidural patching of CSF leaks with fibrin glue has not been established.

Given the increased utilization of epidural patching with fibrin glue, it has become important to understand the predisposing factors to its potential complications. The purposes of this study are to determine the incidence of hypersensitivity reactions to EBP with fibrin glue and to determine if there are specific factors regarding procedural technique, patient, or demographic characteristics that may be associated with increased risk.

MATERIALS AND METHODS

Study Design and Total Patient Cohort

This single-center retrospective cohort study included all patients who received fibrin glue patching for the treatment of SIH or iatrogenic CSF leaks at Duke University Medical Center from January 1, 2009, through June 5, 2022. Patients were excluded if they did not receive fibrin glue as part of their patching procedure or if they had prior patching procedures at outside institutions with incomplete information leading to uncertainty about prior exposure to fibrin glue. Patients were identified via manual review of departmental procedure logs in addition to procedure schedules in the electronic medical record (Epic Systems). Data were collected by reviewing both imaging studies in PACS and procedural reports via electronic medical records. Supplemental searches were conducted via the DEDUCE and SLICER DICER query systems embedded in Epic to confirm the complete identification of all appropriate candidate patients.

The incidence of hypersensitivity reactions was calculated for the total cohort at a per-patient and per-procedure level. A nested case-control design was then used to select a matched control group. Patient demographics and procedure-specific variables, including a history of prior EBP with fibrin glue (prior exposure), the number of days since prior fibrin glue exposure, and the presence of inadvertent intravascular injection during the epidurogram, were collected. Per institutional practice, which was derived from premedication regimens in the setting of iodinated contrast allergies, all patients in the cohort received 50 mg of intravenous diphenhydramine (Benadryl) 1 hour before patching if previously exposed to fibrin glue.[13]

Case-Control Cohort

For the nested case-control component of this study, cases were identified from the broader retrospective cohort, defined by the patient experiencing a hypersensitivity reaction to fibrin glue patching (see definition of a hypersensitivity reaction below).[14] The charts of all patients with reactions were checked independently by 2 authors to confirm that they met the criteria for a hypersensitivity reaction before inclusion in the case group. Disagreements were adjudicated by a board-certified, fellowship-trained allergy/immunology physician with greater than 15 years of post-training experience in hypersensitivity reactions. Cases were matched 1:3 with control patients who did not have hypersensitivity reactions to fibrin glue patching. Matching was based on the total number of epidural patching procedures with fibrin glue performed in each patient. The last procedure performed in each matched control was selected to compare against the case procedure. For example, a hypersensitivity reaction during a third fibrin glue patching procedure was matched to a control patient's third fibrin glue patching procedure.

CT Fluoroscopy-Guided Epidural Patching Procedure

All patching procedures were performed in the same manner as previously described.[15] In brief, CT fluoroscopic guidance was used to direct percutaneous needle placement into the epidural space to deliver patching material. In general, percutaneous needle approaches were either interlaminar, transforaminal, or ventral transforaminal.[5,16,17] Appropriate needle-tip positioning and exclusion of inadvertent intravascular location were confirmed via the "double tap" technique, as previously described, before delivering patching material.[18] Needle-tip positioning was adjusted during the epidurogram if intravascular injection was detected. Therefore, procedures during which intravascular injection was detected likely reflect those where this event was not recognized (Figure). In our practice, when treating CSF-venous fistulas (CVFs), we inject patching material into the adjacent epidural space and do not intentionally attempt intravenous patching, as reported by other authors. All procedures included in this study included the use of fibrin glue (Tisseel, Baxter Healthcare) with or without sterile autologous blood. Fibrin glue is a 2-component sealant made from pooled human plasma. When combined, the 2 components, sealer protein and thrombin, mimic the final stage of the blood coagulation cascade. Fibrin glue is currently used as part of the standard of care treatment at many tertiary referral centers for patients with CSF leaks.

Hypersensitivity Reactions

Hypersensitivity reactions were defined in accordance with a severity grading system for acute allergic reactions developed by allergy and emergency medicine experts and endorsed by the European Academy of Allergy and Clinical Immunology that includes clinical criteria defined by neurologic, cardiac, respiratory, mucosal, skin, and gastrointestinal symptoms.[14] We followed the recommendations outlined in this statement and the severity of hypersensitivity reactions was based upon the proposed 5-tiered grading system and simplified by splitting into 2 categories: 1) mild or moderate reaction and 2) severe (including anaphylaxis).

Mild to moderate reactions were defined as any mild cardiovascular (weakness, dizziness, palpitations), neurologic (confusion, drowsiness), respiratory (chest tightness, dyspnea), or gastrointestinal symptoms (nausea, abdominal pain, emesis, diarrhea) or mild to moderate skin or mucosal symptoms (mild soft palate or tongue swelling, itching or tingling in the mouth, eye irritation).

Severe reactions/anaphylaxis were defined as moderate to severe cardiovascular, neurologic, or respiratory reactions or severe mucosal reactions (severe tongue, soft palate, and/or uvula swelling). Severe cardiovascular symptoms included hypotension,

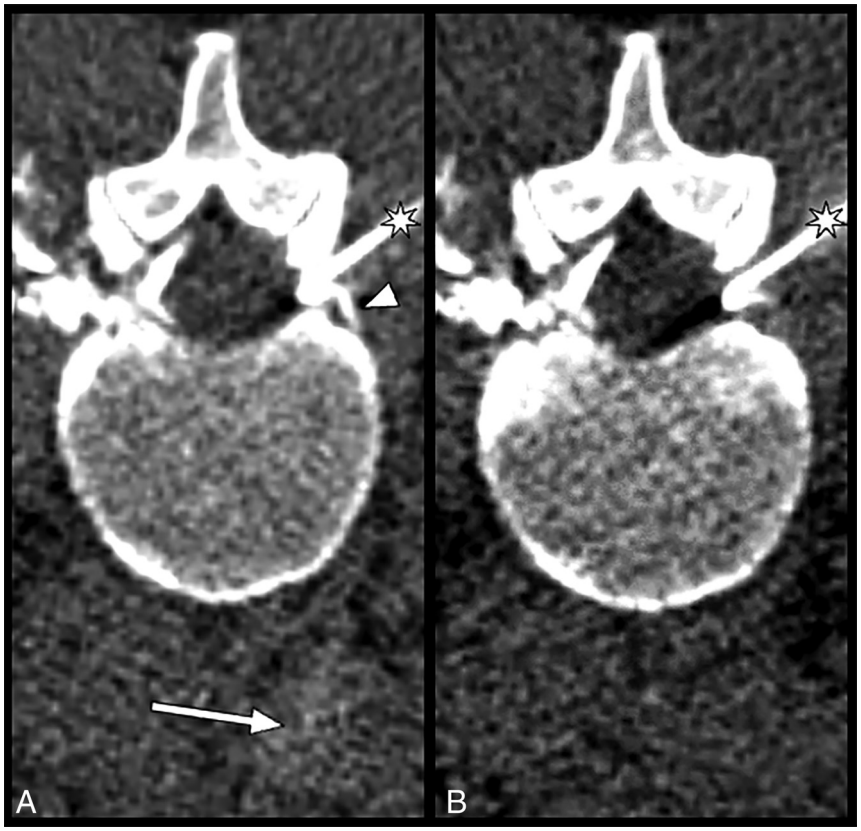

FIGURE. Subtle inadvertent intravenous injection was not recognized during the patching procedure. A 58-year-old woman with an iatrogenic CSF leak secondary to an intrathecal pump placement at L1/2. CT fluoroscopy-guided bilateral transforaminal approach ventral epidural blood and fibrin glue patches were performed. The left side had already been completed. *A*, Axial CT fluoroscopic image during right posterior oblique approach needle placement (*star*) during the initial epidurogram with acquisition immediately after contrast media injection. Note that curvilinear contrast extends anterolaterally from the neuroforamen suggesting intravascular injection (*arrowhead*). There is also a subtle blush of contrast in the inferior vena cava (*arrow*). *B*, Subsequent axial CT fluoroscopic image acquired 1–2 seconds later. There is rapid contrast washout in both structures consistent with an inadvertent intravenous injection.

Table 1: Incidence of hypersensitivity reactions per procedure number

Procedure Number	Patients with Hypersensitivity Reaction during Procedure	Total Number of Patients Undergoing[a]	Incidence (per Patient)
1	0	1574	0
2	8	600	1.33%
3	1	272	0.37%
4	4	150	2.67%
5	1	103	0.97%
6	0	61	0
7	0	45	0
8	0	37	0
9	0	32	0
10	0	24	0
11	0	22	0
12	1	20	5.00%

[a] Total number of patients that had at least this number of procedures.

tachycardia, mottling, cyanosis, and cardiac arrest. Severe neurologic symptoms included changes in Glasgow Coma Scale, altered mental status, lethargy, and seizures. Severe respiratory symptoms included shortness of breath, coughing, increased work of breathing, stridor, and hypoxemia. The timeframe of reaction was defined as the onset of no greater than 72 hours after administration of fibrin glue.

Statistics

In the total patient cohort, the incidence of hypersensitivity reactions was reported on both a per-procedure and per-patient basis. For the nested case-control portion of this study, patient and procedural characteristics were summarized descriptively by using means, standard deviations, and ranges for continuous variables and counts and frequencies for categoric variables. To test for associations between the development of a hypersensitivity reaction and either patient or procedural factors, we fit univariable conditional logistic regression models presented as OR and 95% CI. Linearity assumptions were assessed for continuous variables, and days since prior fibrin glue exposure were log transformed. Complete case analyses were used for missing data. *P* values with and without Bonferroni correction for multiple testing were presented. Commercially available software was used for statistical analysis (R 4.4.0, http://www.r-project.org, and SAS 9.4, SAS Institute), and an α level of .05 was used for statistical significance.

RESULTS

Total Patient Cohort

A total of 3065 CT-guided epidural patching procedures by using fibrin glue were identified in 1574 individual patients during the study period. Of the 1574 patients, the mean age at first procedure was 47.5 years (SD: 14.9, range: 5–90), and 67.2% (1058/1574) were women. There were 15 hypersensitivity reactions to EBP with fibrin glue for an incidence of 0.49% (15/3065) per procedure and 0.95% (15/1574) per patient.

Hypersensitivity reactions never occurred during the first EBP with fibrin glue. Most occurred during the second procedure (Table 1).

Case-Control Cohort

The 15 cases were matched (1:3) by using the methods described above to select a control group of 45 patients. Demographics of the 2 groups are presented in Table 2. Case patient hypersensitivity reactions were categorized into 2 main groups, including mild/moderate and severe. Eight of the case patients (53%) experienced severe reactions; specifically, all patients had anaphylaxis to fibrin glue. The remaining 7 case patients (47%) had mild to moderate hypersensitivity reactions. Anaphylactoid reactions were treated with epinephrine and IV steroids, with some cases requiring short-

Table 2: Patient demographics of case and matched control group procedures

Variable	Case Procedures (n = 15)	Matched Control Procedures (n = 45)
Age at procedure (y)[a]	38.0 ± 14.2 (6.9–60.7)	50.2 ± 15.2 (17.6–81.6)
Female[b]	12/15 (80)	33/45 (73.3)
BMI (kg/m^2)[c]	22.3 ± 4.5 (14.7–30.8)	27.2 ± 5.5 (16.4–40.6)
Race[b]		
White	13/15 (86.7)	40/45 (88.9)
Asian	0	1/45 (2.2)
Black	0	3/45 (6.7)
Missing	2/15 (13.3)	1/45 (0.2)
SIH diagnosis (ICHD-3)[b]	9/15 (60)	25/45 (55.6)
CSF leak type[b,d]		
Dural tear	2/9 (22.2)	8/25 (32)
Diverticular	3/9 (33.3)	3/25 (12)
CSF-venous fistula	1/9 (11.1)	9/25 (36)
Indeterminate	3/9 (33.3)	5/25 (20)
Previous exposure to aprotinin[b]	15/15 (100)	44/45 (97.8)
History of other drug allergies[b]	9/15 (60)	29/45 (64.4)
Severity of other drug allergies[b]		
Grade 1, 2, 3	5/15 (33.3)	21/45 (46.7)
Grade 4, 5	2/15 (13.3)	7/45 (15.6)
Unknown	8/15 (53.3)	17/45 (37.8)
History of anaphylaxis to other drugs[b]		
Yes	5/15 (33.3)	26/45 (57.8)
No	2/15 (13.3)	5/45 (11.1)
Unknown	8/15 (53.3)	14/45 (31.1)

Note:—ICHD-3 indicates International Classification of Headache Disorders, 3rd Edition.
[a] Continuous variables are presented as mean ± standard deviation (range).
[b] Categoric variables are presented as numerator/denominator (percentage).
[c] BMI was missing for 3 control procedures.
[d] Only includes patients with ICHD-3 SIH diagnosis.

Table 3: Procedural characteristics for case and matched control group procedures

Variable	Case Procedures (n = 15)	Matched Control Procedures (n = 45)
Number of patches[a]	2.9 ± 1.6 (1–6)	2.7 ± 1.5 (1–10)
Inadvertent intravascular (venous) injection[b]	6/15 (40)	4/45 (8.9)
Days between index procedure and prior fibrin glue exposure	324.9 ± 766.8 (18–3072)	389.2 ± 454.0 (1–1668)
Needle approach for injectionb		
Transforaminal	8/15 (53.3)	20/45 (44.4)
Interlaminar	3/15 (20)	3/45 (6.7)
Ventral transforaminal	0/15 (0)	2/45 (4.4)
Mixed/multiple	4/15 (26.7)	20/45 (44.4)

[a] Continuous variables are presented as mean ± standard deviation (range).
[b] Categoric variables are presented as numerator/denominator (percentage).

term hospital admission. All patients recovered completely. Most patients experiencing mild/moderate reactions and all patients with anaphylaxis received blood alone for any future patching procedures. Rarely did those in the mild/moderate group continue to receive fibrin glue, in which case the premedication regimen was escalated. One patient with a mild reaction continued to have breakthrough hives despite premedication with IV steroids and an increased dose of Benadryl.

Procedural characteristics for each group can be found in Table 3. Univariable associations between potential covariates predictive of the development of a hypersensitivity reaction are presented in Table 4. The conditional logistic regression models found higher odds for hypersensitivity reactions in younger patients (OR 0.95 [0.91–0.99], P = .011), in those with a lower BMI (OR 0.82 [0.71–0.96], P = .003), and during procedures with inadvertent intravenous injections (OR 5.44 [1.34–22.01], P = .014). For an increase in age of 1 year, the odds of an allergic reaction to the procedure decreased by 4.8%. For a unit increase in BMI, the odds of an allergic reaction to a procedure decreased by 17.6%. The odds of an allergic reaction to a procedure when there was an inadvertent intravenous injection were 5.45 times the odds of an allergic reaction when there was no inadvertent intravenous injection. However, after Bonferroni correction for multiple comparisons, only BMI remained statistically significant (P = .036).

DISCUSSION

We found an incidence of 0.49% for hypersensitivity reactions to epidural patching with fibrin glue in a large cohort of 3065 procedures performed in 1574 patients. Notably, hypersensitivity reactions never occurred during the initial exposure to fibrin glue; they always occurred on a subsequent procedure. Increased patient age (OR 0.95 [0.91–0.99], P = .011) and BMI (OR 0.82 [0.71–0.96], P = .003) were associated with lower odds of a hypersensitivity reaction, and there was a greater likelihood of a reaction in the setting of an intraprocedural inadvertent intravenous injection (OR 5.44 [1.34–22.01], P = .014).

Table 4: Associations between covariates and a hypersensitivity reaction

Variable	OR (95% CI)	*P* Value	Adjusted *P* Value[a]
Age	0.95 (0.91, 0.99)	.01	.13
Men vs women	0.67 (0.15, 2.91)	.59	1
BMI ($n = 57$)	0.82 (0.71, 0.96)	.003	.04
SIH diagnosis	1.17 (0.39, 3.51)	.78	1
CSF leak type ($n = 34$)		.52	1
Diverticular vs dural tear	4.25 (0.33, 55.74)		
CSF-venous fistula vs dural tear	0.53 (0.04, 7.06)		
Indeterminate vs dural tear	0.97 (0.10, 9.31)		
Number of patches	1.07 (0.75, 1.54)	.71	1
Inadvertent intravascular injection	5.44 (1.34, 22.01)	.014	.17
Days between index procedure and prior fibrin glue exposure (log transformed)	0.79 (0.54, 1.17)	.23	1
History of other drug allergies	0.81 (0.23, 2.90)	.75	1
Severity of other drug allergies		.56	1
Grade 4/5 vs grade 1/2/3	1.13 (0.18, 7.00)		
Unknown	2.03 (0.53, 7.81)		
History of anaphylaxis to other drugs		.26	1
Yes vs no	1.93 (0.29, 13.00)		
Unknown vs no	2.88 (0.77, 10.81)		

[a] Bonferroni corrected *P* values.

Note:—Race, needle approach, and prior exposure to aprotinin were unable to be assessed as the model did not converge (zero cell counts).

Our findings indicate proceduralists should be particularly vigilant about the development of a hypersensitivity reaction in younger patients with a lower BMI during repeat EBP procedures and should be cautious about inadvertent intravascular injections during the procedure. Given these findings, it has been our long-standing practice to prophylactically premedicate patients receiving repeat fibrin glue EBP with intravenous Benadryl before the procedure.

Descriptions of the use of fibrin glue to improve the efficacy of epidural patching of CSF leaks have been present in the literature for over 20 years.[9,10,19] While the use of fibrin glue is now common at SIH referral centers, the literature on hypersensitivity reactions during EBP with fibrin glue is sparse. Schievink et al[19] first reported on the percutaneous injection of fibrin glue to treat spontaneous intracranial hypotension in a case series of 4 patients in 2004. This group subsequently reported the occurrence of 2 anaphylactic reactions during EBP with fibrin glue.[6] To our knowledge, our study represents the largest reported cohort of EBP with fibrin glue to date and thereby provides a better understanding of the incidence of hypersensitivity reactions during these procedures and potential variables that may increase the probability of such an event.

The primary safety concern when using fibrin glue during percutaneous epidural patching is the potential for an allergic reaction. Aprotinin, a proteinase inhibitor, is a component within fibrin glue products because it helps to prevent lysis of the created clot. Aprotinin has been used for hemostasis in cardiac, gastrointestinal, and neurosurgery for many years. Unfortunately, aprotinin can cause allergic reactions in some patients. The literature suggests that several factors may affect the likelihood of such reactions. First, the mechanism of application appears to correlate with the probability of an event. Intravascular injection, in particular, increases the risk. One review found that 92% of all hypersensitivity reactions during surgery were reported in patients that had received product intravascularly.[20] Previous exposure to aprotinin (fibrin glue) has also been reported to increase the risk of an allergic reaction.[21] Literature review reveals that 68% (30/44) of anaphylactic reactions occurred after re-exposure within a 3–6 month window after the initial application.[22] For example, intravascular injection of these products during cardiac surgery raised the rate of allergic reaction from less than 0.1% to 1.8%.[12] It should be noted that, based on this prior literature, both the manufacturer of fibrin glue and the Food and Drug Administration recommend against intravascular use.[23,24]

More recently, several authors have advocated for the injection of fibrin glue adjacent to the junction of the meningeal diverticulum and draining vein associated with CVFs, demonstrating that this improves efficacy.[7,25] However, our study suggests that proceduralists should operate with caution when attempting these approaches and should be mindful of inadvertent intravascular injection of fibrin glue, which may predispose to allergic reactions, since our method of injecting into the epidural space adjacent to the target CVF may have allowed for lower complication rates than may be seen with these alternative approaches. Other authors have previously reported a series that contained 30 patients with intravascular injections of fibrin glue, none of whom experienced hypersensitivity reactions.[24] The discrepancy may be due to differences in procedural technique or could represent type II error given the smaller number of cases in the prior study ($n = 30$) and the large number of cases in the current study ($n = 3065$). The incidence of 0.49% found in our study would mean that 200 cases are needed on average to see an allergic reaction. However, it is important to remain mindful that the potential for allergic reactions during patching with fibrin glue is possible no matter the underlying CSF leak subtype. In our group's experience, inadvertent intravascular injections can occur when treating ventral CSF leaks and dural tears, as well as CVFs.

Reasons as to why lower BMI and younger age may predispose to hypersensitivity reactions are less clear. One possible consideration is that these patients may have a higher attenuation of vascularity, consequently increasing the risk of inadvertent intravascular injection. Further investigation into these findings is needed to better understand the reason for this relationship.

There are several limitations to this investigation. First, in this large patient cohort, there were still a relatively small number of procedures with an allergic reaction. Thus, the study may be

underpowered to detect significant differences between the case and control procedures that may increase the odds of an allergic reaction. As with any case-control study design, there may be unrecognized additional covariates that increase the likelihood of an allergic reaction that were not tested, and interpretations are limited due to the retrospective observational nature of the study. Further, this study included data from a single institution where there is homogeneity in the procedural technique. This could limit generalizability to other centers. Differences in procedural technique, notably intentional injection of fibrin glue into paraspinal veins to treat CVFs, could increase the incidence of allergic reactions. In this study, the identification of inadvertent intravascular injections was performed through a retrospective review of the contrast epidurogram on intraprocedural imaging. While our team does not change the needle-tip position between the epidurogram and the injection of fibrin glue, inadvertent intravascular injections may be more accurately characterized if contrast had been mixed directly with the fibrin glue (which is not our standard practice). Additionally, while unlikely, it is possible that some of the hypersensitivity reactions occurred secondary to other medications used during the procedure, such as iodinated contrast or those provided for moderate sedation. Further, our group premedicates all patients receiving repeat EBP with fibrin glue with intravenous Benadryl. This prophylactic measure may have reduced the rate of hypersensitivity reactions, and other groups that do not employ this measure routinely could have an elevated incidence of allergic reactions. Finally, it is important to note that there are formulations of fibrin glue available that do not contain aprotinin. For this reason, it is possible that these products may have a lower incidence of hypersensitivity reactions. This topic could serve as an area of future comparative research.

CONCLUSIONS

Our study of a large cohort of patients with CSF leak treated with epidural patching procedures containing fibrin glue revealed a 0.49% incidence of hypersensitivity reactions, none occurring at first exposure to fibrin glue. These reactions were significantly more likely in patients with a lower BMI and may be more prevalent in younger patients. They are also more likely in the setting of an inadvertent intravenous injection during the procedure. Future research should investigate the role of needle-tip positioning and its proximity to the paraspinal veins, particularly in the setting of CVFs, and how this may affect hypersensitivity reaction rates.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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