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Pain Reduction Following Eptacog Beta Treatment of Bleeding Episodes in Adolescents and Adults With Haemophilia A or B Complicated by Inhibitors

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ABSTRACT

Introduction: Joint and muscle bleeding in persons with haemophilia (PwH) causes acute pain, an important patient-reported outcome for evaluating treatment response. Eptacog beta is a recombinant activated human FVII bypassing agent approved for the treatment and control of bleeding in PwH A or B with inhibitors (PwHABI) ≥12 years using initial dose regimens (IDRs) of 75 or 225 μg/kg.

Aim: To evaluate pain reduction in PwHABI who treated bleeding episodes (BEs) with eptacog beta during the PERSEPT 1 trial.

Methods: PwHABI were randomly assigned to 75 or 225 μg/kg IDRs for BE treatment. Participants reported pain levels at predefined treatment evaluation timepoints using a visual analogue scale (VAS). Pain analyses were stratified by age, IDR assignment, and baseline pain levels. The diagnostic potential for using VAS pain score reductions to assess treatment response was explored using receiver operating characteristic (ROC) analysis.

Results: Five adolescents and 22 adults treated 468 BEs. Mean VAS scores decreased 30%–58% from baseline at 3 h post-initial eptacog beta infusion amongst age and IDR categories, with further VAS score reductions observed through 24 h. PwHABI with high baseline BE pain showed larger absolute VAS score reductions before ending treatment than PwHABI experiencing mild BE pain. The optimum VAS score percentage reduction cutoff for predicting treatment outcomes was 44%.

Conclusion: Pain relief over 24 h was observed with eptacog beta treatment across IDR and age categories. This post hoc study demonstrates that percentage reduction from baseline VAS score influences perception of bleed resolution and can predict treatment outcomes.

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1 | Introduction

Acute and chronic pain are pervasive features of joint and muscle bleeding episodes (BEs) that are frequently experienced by persons with haemophilia (PwH). Acute pain is an important symptom that guides the clinical management of BEs, as the onset of pain usually precedes other overt signs of bleeding and signals the need for prompt treatment [1–3]. In addition, alleviation of pain following treatment can indicate resolution of bleeding and motivate a decision to end treatment [2]. Recurrent haemorrhages in joints of PwH lead to synovitis, progressive cartilage and bone destruction, mobility limitations, and an erosion of the daily quality of life that becomes marked by chronic, debilitating pain [3–5]. Morfini and colleagues found that PwH A or B with inhibitors (PwHABI) report more joint pain than PwH without inhibitors [6]. Following a public meeting with haemophilia community members in 2014, the US Food and Drug Administration (FDA) concluded that pain eradication is a significant endpoint of treatment efficacy in haemophilia [7].

Eptacog beta is a recombinant activated FVII that is approved in the US (SEVENFACT; HEMA Biologics and LFB SA) [8] and in the EU and UK (CEVENFACTA; LFB SA) [9] for the treatment and control of BEs in PwHABI ≥12 years of age, as well as in the EU and UK for the prevention of bleeding during major or minor surgery in the same population. The pivotal PERSEPT 1 trial (NCT02020369) included 27 male PwHABI ≥12 years old who were treated with 468 BEs with eptacog beta [10]. Pain levels in this trial were recorded at the onset of bleeding and periodically during eptacog beta treatment using a visual analogue scale (VAS). The VAS has been frequently used to assess acute pain intensity experienced by patients in diverse clinical settings and populations, including individuals with haemophilia [11, 12].

In this post hoc analysis of PERSEPT 1 trial data, we characterized changes in pain intensity through 24 h following the initial eptacog beta infusion for BE treatment in adolescent and adult PwHABI. We also determined clinically meaningful levels of pain reduction, as defined by the VAS score decreases observed when decisions to end treatment were made, in the PwHABI care setting. These observed pain reductions may potentially inform the development of endpoints for substantive pain relief when designing clinical trials of bypassing agents. Finally, based on receiver operating characteristic (ROC) analysis using treatment efficacies and concomitant pain decreases observed with eptacog beta administration, we offer a clinical tool for gauging the likelihood of successful BE resolution for given threshold pain reduction levels achieved following BE treatment in PwHABI.

2 | Methods

The PERSEPT 1 trial design has been previously described [10]. In brief, adolescent and adult PwHABI (12 to <18 and ≥18 years of age, respectively; age range 12–54 years) in PERSEPT 1 were randomly assigned to either 75 or 225 μg/kg initial dose regimens (IDRs) for treatment of BEs of all severity (mild, moderate and severe). PwHABI treated BEs with an initial dose of 75 or 225 μg/kg eptacog beta (depending on IDR assignment) followed by 75 μg/kg eptacog beta at prespecified intervals as needed based on haemostasis assessment (Table 1). PwHABI were crossed over to the alternate IDR every 3 months without a washout period. The BE treatment success proportion at a given timepoint post-initial eptacog beta infusion was defined in this study as the proportion of BEs with a patient-reported 'good' or 'excellent' efficacy assessment (based on a 4-point haemostasis evaluation scale of 'excellent', 'good', 'moderate' and 'none'; Table 1). Pain levels were evaluated by the study participants at the onset of bleeding prior to eptacog beta treatment (baseline) and at each treatment evaluation timepoint (including at 12 and 24 h) using a 0 to 100 mm VAS (0 mm corresponding to no pain; 100 mm corresponding to worst possible pain) [10]. Except where noted, BEs requiring analgesics were excluded from the analyses described here.

Post hoc VAS pain score analyses were stratified by age group (adolescent or adult) and IDR assignment (75 or 225 μg/kg). VAS scores of 0 mm at a given timepoint were included in all pain score analyses unless specified otherwise. Clinically meaningful reduction in acute BE pain was defined as the observed VAS score decrease from baseline at the timepoint when PwHABI decided to end BE treatment. As an association between baseline pain levels and the pain reductions needed to achieve meaningful pain relief has been noted in other clinical settings [11, 13], the impact of baseline BE pain on VAS pain score decreases associated with clinically meaningful pain reduction in PwHABI was also examined. Towards this end, BEs were assigned to lower, middle, and upper VAS range groups (0–33 mm, 34–66 mm, and 67–100 mm, respectively) according to the baseline VAS score recorded at the onset of bleeding. The thresholds delimiting these VAS score groups were chosen to provide three categories of equal intervals across the VAS, without assumptions of a strict correspondence to mild, moderate, or severe BE pain intensity being experienced by individual PwHABI. Mean (standard deviation; SD) VAS scores at baseline and at timepoints when PwHABI ended eptacog beta treatment were calculated for BEs in age and VAS score groups. In addition, mean (SD) VAS score reductions from baseline observed at timepoints when BE treatment ended were also calculated for BEs in age and VAS score groups.

The diagnostic potential for using the VAS score percentage decreases from baseline to assess treatment outcomes was examined using ROC analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) results for a given VAS score percentage reduction cutoff value were tabulated in a 2 × 2 table using pain reduction levels and treatment outcomes at 3 h post-initial infusion of eptacog beta (Table 2). Sensitivity and specificity calculations were repeated for a range of VAS score percentage reduction cutoff values to generate an ROC curve. The VAS score percentage reduction cutoff that yielded optimal diagnostic performance was identified by minimizing the Euclidean distance between the ROC curve and the coordinate (0, 1) and maximizing Youden's J-statistic (represented graphically as the height of a cutoff point above the 45° line) [14]. The area under the ROC curve (AUC) was used to assess the overall performance of the diagnostic test, with AUC values between 0.8 and 0.9 indicating good performance and values ≥0.9 indicating excellent performance [14]. ROC analysis was conducted using SAS version 9.4.

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TABLE 1 | Four-point haemostasis assessment scale for bleeds of all severity in PERSEPT 1 [10].

Haemostasis assessment	Description	Treatment response
Excellent	• Full pain relief and cessation of objective signs of bleeding	**Satisfactory**
	• No continuation of eptacog beta required	
Good	• Symptoms of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal haemorrhage) were largely reduced, but had not completely disappeared	
	• No continuation of eptacog beta required, given the improvement of the symptoms	
Moderate	• Some response was noticed (e.g., pain decreased or bleeding signs improved), but bleeding continued	**Unsatisfactory**
	• Continuation of eptacog beta required	
None	• No noticeable effect of treatment on the BE, or worsening of the patient's condition	
	• Continuation of eptacog beta required	

Abbreviation: BE, bleeding episode.

TABLE 2 | Calculations of sensitivity, specificity, PPV, and NPV for a given VAS score percentage reduction from baseline at 3 h using a 2 × 2 table.[a]

Percentage decrease in VAS score at 3 h	BEs with 'excellent' or 'good' haemostasis evaluation	BEs with 'moderate' or 'none' haemostasis evaluation	Total
≥44%	$a = 145$	$b = 24$	169
<44%	$c = 36$	$d = 132$	168
Total	181	156	$n = 337$[b]

Abbreviations: BE, bleeding episode; NPV, negative predictive value; PPV, positive predictive value; VAS, visual analogue scale.

[a]Values calculated for a cutoff value of 44% reduction in VAS pain score from baseline at 3 h post-initial eptacog beta infusion. Sensitivity: a/(a + c) = 80.1%. Specificity: d/(b + d) = 84.6%. PPV: a/(a+b) = 85.8%; NPV: d/(c+d) = 78.6%.

[b]n = total number of BEs available for sensitivity, specificity, PPV, and NPV calculations.

3 | Results

3.1 | Study Population and Analgesic Administration

Twenty-two adults and 5 adolescents treated 468 BEs (465 mild or moderate and 3 severe BEs) with eptacog beta during PERSEPT 1, with 460/468 (98.3%) being treated in a home setting. Analgesics were given to relieve pain for 48/468 (10.3%) of BEs, and a medication from the opioid class was given in 42/48 (87.5%) instances where an analgesic was used. Mean VAS scores for BEs where analgesics were given during eptacog beta treatment decreased from baseline over 24 h and were higher than corresponding mean VAS scores for BEs where analgesics were not administered (Figure S1), although a meaningful statistical comparison was precluded owing to the limited number of BEs where analgesics were given. To better assess VAS score changes that were associated solely with eptacog beta administration, the 48 BEs where analgesics were used for pain management were excluded from further analysis. VAS score changes were thus evaluated for 420 BEs (84% in joints) where no analgesics were administered, with 82 BEs being experienced by adolescents and 338 BEs by adults. No PERSEPT 1 participants were receiving bypassing agent or emicizumab prophylaxis.

3.2 | Pain Reduction Through 24 h Post-Initial Eptacog Beta Infusion

Mean (SD) BE baseline VAS pain scores varied from 26.5 (22.1) to 42.2 (23.8) mm across four age and IDR subgroups (Figure 1A). At 3 h post-initial infusion of eptacog beta in the adolescent group, mean (SD) VAS pain score decreases from baseline were 19.3 (19.0) mm in the 75 μg/kg IDR group and 15.3 (13.7) mm in the 225 μg/kg IDR group, corresponding to VAS score decreases from baseline of 47% and 58%, respectively. In the adult group, mean (SD) VAS score decreases from baseline at 3 h were 12.5 (10.8) mm in the 75 μg/kg IDR group and 18.1 (16.7) mm in the 225 μg/kg IDR group, corresponding to VAS score decreases from baseline of 30% and 49%, respectively. At 12 h, mean (SD) VAS pain scores had dropped to values varying from 1.1 (5.4) to 7.2 (13.7) mm across all age and IDR subgroups. Mean (SD) VAS pain scores decreased further at 24 h across all age and IDR subgroups, falling to values varying from 0.0 (0.0) to 2.0 (6.8) mm (Figure 1A). BE treatment success proportions accompanying the VAS score decreases at 3 h in the adolescent group were 44% and 75% in the 75 μg/kg and 225 μg/kg IDR groups, respectively. In the adult group, the corresponding treatment success proportions at 3 h post-initial eptacog beta infusion were 31% and 91% in the 75 and 225 μg/kg IDR groups, respectively. Overall, treatment success proportions

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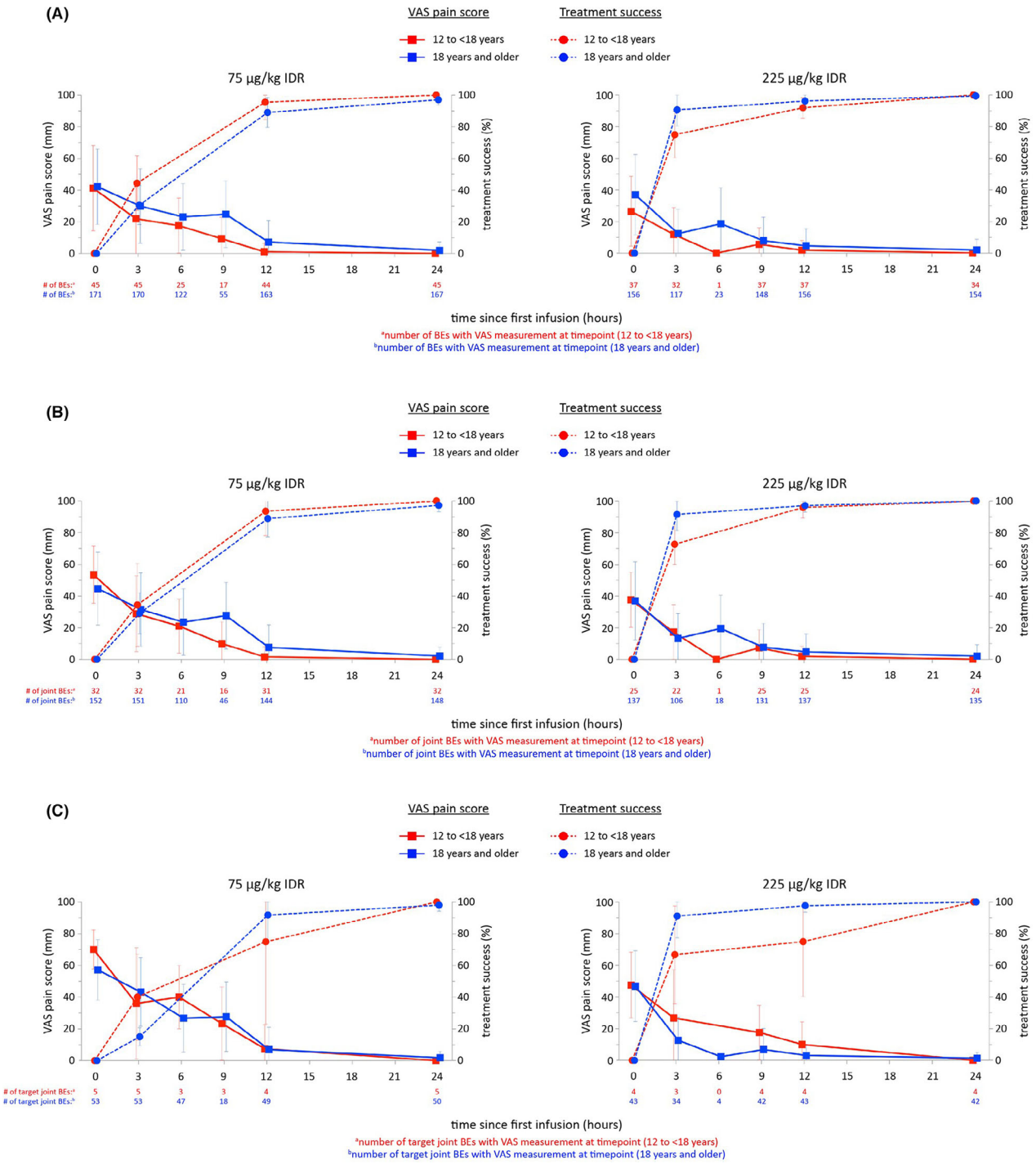


FIGURE 1 | VAS pain score (left y-axis) and treatment success proportions (right y-axis) versus time with eptacog beta treatment for (A) all BEs, (B) joint BEs, and (C) target joint BEs in PERSEPT 1, where analgesics were not administered. The number of BEs with VAS measurements at each timepoint for adolescents and adults is indicated below the x-axis in red and blue, respectively. Error bars indicate standard deviations and 95% confidence intervals for mean VAS score measurements and treatment success proportions, respectively. A target joint was defined as a joint in which recurrent bleeding had occurred on four or more occasions during the previous 6 months, or one in which 20 lifetime BEs had occurred. BE, bleeding episode; IDR, initial dose regimen assignment; VAS, visual analogue scale.

increased as mean VAS pain scores decreased over time, with treatment success proportions ranging between 89% and 96% at 12 h and 97% and 100% at 24 h across all age and IDR subgroups (Figure 1A). VAS pain scores and treatment success proportions for joint BEs and target joint BEs showed similar trends through 24 h (Figures 1B and 1C).

3.3 | Assessment of Clinically Important Changes in Acute BE Pain

VAS score changes between successive timepoints and corresponding updates in patient-reported haemostasis assessments were recorded to identify changes in pain levels that are

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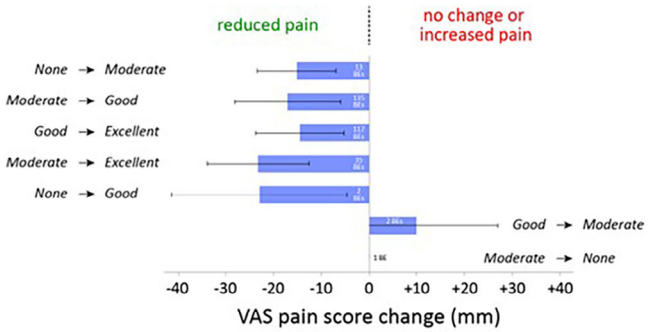


FIGURE 2 | Mean VAS pain score changes observed when haemostasis assessments were updated by PwHABI in PERSEPT 1 (all age and IDR subgroups combined). Error bars indicate standard deviations for mean VAS score changes. The number of BEs for each type of haemostasis assessment update is indicated. PwHABI, persons with haemophilia A or B and inhibitors. BE, bleeding episode; VAS, visual analogue scale.

clinically meaningful in the PwHABI acute BE care setting. The overall mean (SD) changes in VAS pain scores observed when PwHABI-reported haemostasis assessments were updated from 'moderate' to 'good' (135 BEs) and from 'moderate' to 'excellent' (35 BEs) for all age and IDR subgroups combined were −17.1 (11.1) mm and −23.3 (10.7) mm, respectively (Figure 2). These haemostasis assessment updates correspond to an improvement in haemostasis response from 'unsatisfactory' to 'satisfactory' (Table 1). Other VAS score changes associated with haemostasis assessment updates are shown in Figure 2.

Clinically meaningful changes in acute BE pain in PwHABI were also assessed through analyses of VAS score decreases observed when decisions to cease BE treatment were made, stratified by baseline VAS score group. The number (percentage) of BEs in the lower, middle, and upper VAS range groups was 177 (42.1%), 166 (39.5%), and 66 (15.7%), respectively. Baseline VAS scores for 11 BEs (2.6%) were not recorded. Mean (SD) pain scores at timepoints corresponding to decisions to end treatment of BEs in the lower, middle and upper VAS categories were 3.4 (6.0), 15.0 (14.0) and 17.3 (16.1) mm, respectively, with associated mean (SD) VAS score reductions from baseline of 10.7 (10.2), 35.2 (15.1) and 58.9 (17.1) mm, respectively (Figure 3A). These results indicate that PwHABI with high baseline pain levels showed larger absolute VAS score reductions before ending treatment than PwHABI experiencing low baseline pain. Although the absolute magnitude of pain score reductions increased with baseline BE pain severity, on a percentage basis, these reductions remained relatively constant (lower VAS range: 75% reduction; middle range: 71%; upper range: 77%; Figure 3A). Mean VAS score reductions across VAS score categories in the adolescent group varied between 10.3 and 71.8 mm (87%–98%), while in the adult group, the corresponding reductions were 10.9–56.3 mm (67%–73%; Figure 3B).

3.4 | Identifying VAS Pain Score Changes and Thresholds That are Predictive of Bleed Resolution

The predictive value of specified VAS score percentage decreases in identifying BEs with satisfactory haemostatic responses (i.e., 'good' or 'excellent') at 3 h was explored using ROC analysis. VAS score percent decreases and haemostasis assessments at 3 h were available for 364 of the 420 BEs. For 27 of these 364 BEs, VAS scores of 0 mm were recorded at both baseline and 3 h post-initial eptacog beta infusion. As a percentage decrease from baseline measurements of 0 mm cannot be defined in these instances, these 27 BEs were excluded from ROC analysis. Most excluded BEs occurred in the nose (10 BEs) or oral cavity (7 BEs).

In all, 337 BEs (91% in joints) were used to calculate sensitivity, specificity, PPV and NPV results for a given VAS score percentage decrease from baseline cutoff at 3 h (Table 2), as well as to generate an ROC curve (Figure 4). A VAS score percentage decrease cutoff of 44% provided optimum values for both the Euclidean distance and Youden's J-statistic (Table 3 and Figure 4), yielding a sensitivity of 80.1% and a specificity of 84.6%. This cutoff point also yielded a PPV of 85.8% and an NPV of 78.6%. Equivalently, BEs with VAS score percent decreases of ≥44% at 3 h post-initial eptacog beta infusion were associated with an 85.8% likelihood of achieving treatment success at that timepoint (i.e., a 'good' or 'excellent' haemostasis evaluation reported), while BEs with VAS score percent decreases of <44% at 3 h had a 78.6% likelihood of needing further treatment (i.e., a 'moderate' or 'none' haemostasis evaluation reported). The AUC was 0.881 (95% confidence interval: [0.844, 0.918]; Figure 4), a finding that is indicative of a meaningful diagnostic test [14].

4 | Discussion

Pain is a personal experience, and pain assessment tools that can adequately capture perceived changes in acute BE pain experienced by PwH during therapeutic intervention are important for evaluating the benefits of any given treatment. The VAS instrument has been used for pain studies in both paediatric and adult populations [11, 12], including in children as young as 4 years [15] and for a variety of clinical conditions including cancer [16], headache [17], dental extraction [18] and extremity trauma [13]. VAS pain scores have shown correlations with measures of functional ability in PwH ages 16–73 years during rehabilitation programs [19]. While acknowledging the limitations of any single assessment tool to measure pain in PwH across all age groups, Humphries and Kessler have supported the use of VAS in pain studies with PwH ages 7 to adult [12]. The VAS instrument may be particularly well suited for assessing pain repeatedly over time with short intervals (hours) between assessments. This characteristic of the VAS is particularly relevant in haemophilia clinical trials where responses to BE treatments are evaluated.

A VAS was used to measure BE pain in PwHABI ages 12–54 during PERSEPT 1. In addition to 0–100 mm VAS measurements, levels of PwHABI pain were indirectly captured via a 4-point haemostasis assessment scale, where PwHABI integrated perceived changes in BE pain (as well as changes in other bleeding symptoms such as swelling and range of motion) into self-reported assessments of eptacog beta treatment efficacy. Substantial or complete BE pain relief was a criterion for a 'good' or 'excellent' haemostasis evaluation, respectively, on the 4-point haemostasis assessment scale (Table 1). Trends in reported VAS pain scores and treatment success proportions over time using these two assessment scales were concordant, with decreasing mean VAS pain scores and increasing eptacog beta

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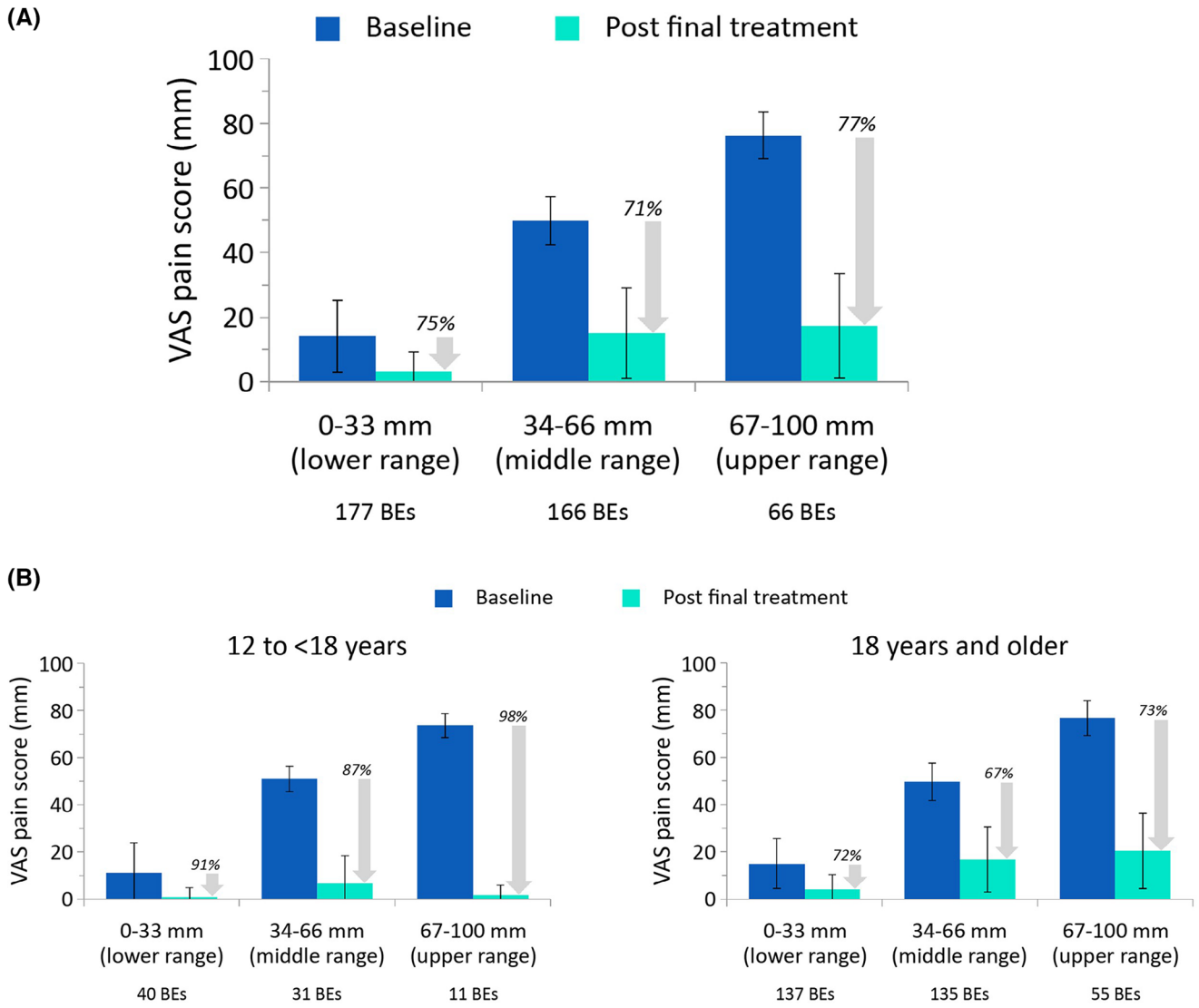


FIGURE 3 | (A) Observed pain reduction at timepoints corresponding to BE resolution and treatment cessation by baseline VAS score. (B) Observed pain reduction at timepoints corresponding to BE resolution and treatment cessation by baseline VAS score and age group. Error bars indicate standard deviations of mean VAS scores. The number of BEs in each subgroup is indicated. BE, bleeding episode; VAS, visual analogue scale.

treatment success proportions (i.e., the proportion of 'good' or 'excellent' responses) observed over 24 h across age groups, IDR assignment groups and bleeding types (Figures 1A–C). Studies of other bypassing agents have described a similar correspondence between PwHABI-reported VAS pain scores and treatment outcomes [20, 21].

Clinically meaningful changes in VAS pain score reported by PwHABI during BE treatment with eptacog beta were evaluated in this post hoc analysis. The mean VAS score changes observed when haemostasis assessments were updated from 'moderate' to 'good' (−17.1 mm) and from 'moderate' to 'excellent' (−23.3 mm), respectively, indicate levels of pain relief that can potentially prompt a change in the clinical management of a BE. Analysis of pain reduction levels from baseline observed at treatment cessation suggests that PwHABI with high levels of baseline pain required larger absolute VAS score reductions before perceiving sufficient pain relief and ending treatment than PwHABI experiencing mild BE pain. This finding is consistent with results from a meta-analysis by Olsen et al. of seven studies (918 patients) that examined the influence of baseline pain on the minimum clinically important difference (MCID) in acute pain. Results from this meta-analysis demonstrated a strong association between baseline pain scores and MCID measurements on an absolute scale, indicating that patients with higher baseline pain need greater pain reduction to perceive relief as compared to patients with lower pain [11].

A clear understanding of acute pain changes that are important to patients can guide appropriate analgesic interventions during clinical care, as well as inform the design of clinical trials where substantive pain relief is a desired treatment outcome. Nonetheless, a single consensus MCID in acute pain across clinical conditions and patient populations has never been identified. Meta-analyses by Olsen et al. of data from 37 acute pain studies (8479 patients) in a variety of clinical settings (none measuring BE pain in haemophilia patients) revealed considerable heterogeneity in absolute MCID measurements (8–40 mm across 29

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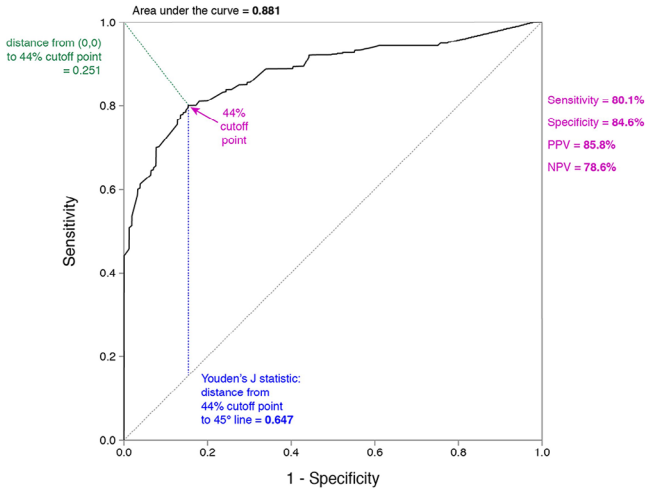


FIGURE 4 | ROC curve analysis based on BE treatment outcomes and VAS score percentage reductions from baseline at 3 h post-initial eptacog beta infusion. The area under the ROC curve and the position on the ROC plot corresponding to the 44% VAS score percentage reduction cutoff are indicated. The values corresponding to sensitivity, specificity, PPV, and NPV (expressed as a percentage) associated with the 44% cutoff are indicated in magenta. The optimized Euclidean distance (green) and Youden's J-statistic (blue) corresponding to the 44% cutoff are also shown. BE, bleeding episode; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; VAS, visual analogue scale.

TABLE 3 | Sensitivity, specificity, and predictive values for several VAS score percentage decrease cutoffs at 3 h post-initial eptacog beta infusion.

Percentage decrease in VAS score at 3 h (% change)	32%	40%	44%	50%	60%	70%
Sensitivity (%)	89.0	83.4	**80.1**	75.7	63.5	53.0
Specificity (%)	65.4	76.3	**84.6**	87.2	93.6	98.1
PPV (%)	74.9	80.3	**85.8**	87.3	92.0	97.0
NPV (%)	83.6	79.9	**78.6**	75.6	68.9	64.3
Euclidean distance	0.363	0.289	**0.251**	0.275	0.370	0.470
Youden's J-statistic	0.543	0.597	**0.647**	0.629	0.571	0.511

Note: Euclidean distances and Youden's J-statistics for given cutoffs are also shown. Results for the optimum cutoff of 44%, as determined by minimizing the Euclidean distance and maximizing Youden's J-statistic for the ROC curve, are indicated in bold.

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; VAS, visual analogue scale.

studies) and in MCID measurements expressed as a relative change (13%–85% across 14 studies) [11]. Methodological variation across studies, differences in MCID definitions and the influence of baseline pain on MCID outcomes (on an absolute scale) were cited as contributing factors to the large heterogeneity in MCID results. Given the span of observed MCID values in different studies, the authors concluded that a single, universally valid MCID could not be meaningfully determined and recommended that interpretation of MCID results take into account the specific clinical setting, methodologies used to determine the MCID and acute pain measured at baseline [11]. Our current post hoc study assessed clinically important acute BE pain reduction in PwHABI across three different baseline VAS pain score categories. VAS score reductions at treatment cessation for these VAS score categories showed a wide variation on an absolute scale (10.9–56.3 mm and 10.3–71.8 mm in adult and adolescent PwHABI, respectively), while the reductions across VAS score groups on a percentage basis showed relative consistency (67%–73% and 87%–98% in adults and adolescents, respectively). The magnitudes of pain relief described in this post hoc analysis are important considerations when designing sufficiently powered trials of bypassing agents in the acute BE care setting, as trial sample sizes must be chosen so that meaningful changes in pain are captured as well as satisfactory haemostatic response.

The pain score cutoff values determined from the ROC curve analysis described here may provide reference points that can inform clinical management of BEs in adolescent and adult PwHABI. The ROC curve analysis identified an optimal VAS score percentage reduction cutoff of 44% that yields a PPV of 85.8% and an NPV of 78.6% (Figure 4). Acute BE management decisions may be based on other cutoff values that yield either higher PPV or higher NPV, depending on the given clinical situation requirements. For example, BE pain intensity reductions at 3 h exceeding a higher cutoff (e.g., 50% or more) would be associated with a higher PPV (Table 3) and a greater likelihood of treatment success being achieved at that timepoint, which may be desirable for certain BE types or locations. The AUC of 0.881 found for the ROC curve generated in the current post hoc analysis indicates that a VAS score percentage reduction from baseline at 3 h can serve as a meaningful diagnostic test with good utility for predicting BE treatment outcomes.

This study has a few identified limitations. The analyses here are confined to acute BE pain experienced by PwHABI in PERSEPT 1, as no information on any underlying chronic pain experienced by study participants was recorded in the trial. Also, any BEs where analgesics were administered were excluded from analyses, and a detailed study of VAS score measurements for BEs where analgesics were given was precluded owing to the limited size of that dataset. Finally, other factors besides pain intensity (e.g., swelling or range of motion limitations) may potentially influence haemostasis assessments and decisions to cease treatment, leading to continued eptacog beta infusions despite achieving substantive pain relief. Nonetheless, based on the pathophysiology of acute hemarthrosis [5], pain intensity and physical manifestations such as heat from the joint, swelling, and range of motion limitations are likely correlative. Furthermore, the concomitant BE treatment success proportion increases with VAS pain score decreases over a 24-h period, indicating that levels of BE pain were an important factor that informed haemostasis assessments by PwHABI and motivated decisions to end eptacog beta therapy.

5 | Conclusion

Along with rapid resolution of bleeding, pain relief is an important treatment outcome when managing acute BEs in PwHABI. Pain reduction was observed at 3 h after initial eptacog beta

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infusion for both IDR groups and in adolescents and adults during PERSEPT 1, with further pain decreases observed at 12 and 24 h. These reductions in pain were achieved without analgesics. In addition, PwHABI with high BE pain at baseline showed larger absolute reductions in VAS score to achieve meaningful pain relief than PwHABI experiencing mild BE pain. This analysis describes clinically important changes in BE pain that may impact haemostasis evaluations and treatment decisions in PwHABI. This information may be useful when designing clinical trials that can adequately measure both substantive pain relief and satisfactory haemostatic response in PwHABI. Finally, based on the ROC analysis using observed pain decreases following eptacog beta treatment, a clinical tool that may aid acute BE management in PwHABI has been provided. Whether such a tool might be extended to aid acute BE management in other clinical populations (e.g., PwH A or B without inhibitors, PwH receiving prophylaxis, or people with mild haemophilia who treat acute BEs) has not yet been explored.

Author Contributions

All of the authors analysed and interpreted the data, and all authors provided critical input and edited the manuscript. All authors reviewed and approved the final submission.

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Ethics Statement

The trial was approved by institutional boards and was conducted in compliance with the Declaration of Helsinki. Written informed consent/assent was obtained.

Conflicts of Interest

T.W.B. has received consulting fees from BioMarin and has served as an advisory board member and received honoraria from BioMarin, Novo Nordisk, Octapharma, and Sanofi. C.M.K. has received consulting fees from Bayer, Genentech, Hema Biologics, Novo Nordisk, Octapharma, Pfizer, Regeneron, Stago Diagnostica, and Takeda; his institution has received funding for research from Bayer, Genetech, Octapharma, and Stago Diagnostica; and he has served on the Data and Safety Monitoring Committees for Bayer and Octapharma. G.C. has received honoraria as a speaker/participant on advisory boards for Bayer, Takeda, CSL Behring, Novo Nordisk, Sobi, Roche, Pfizer, LFB, BIOVIIIx, and BioMarin. C.H. has received research funding from Bayer, BioMarin, CSL Behring, Novo Nordisk, Pfizer, Shire/Takeda, and Sobi; and has received honoraria and speaker bureau fees from Bayer, CAF-DCF, CSL Behring, Hoffmann-La Roche, LFB, Novo Nordisk, Octapharma, Pfizer, Shire/Takeda, Sobi, and uniQure. V.J.Y. has received consulting fees from Grifols, Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda, Bayer, CSL Behring, Pfizer, BioMarin, Sanofi, and Sobi; has received honoraria from Grifols, Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda, Bayer, CSL Behring, Pfizer, Sanofi, and Sobi; and has received research funding from Grifols, Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda, Bayer, CSL Behring, Pfizer, Sanofi, and Sobi. J.M. has received research grants from BioMarin, Catalyst Biosciences, CSL, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Spark and uniQure; has served as a consultant or member of the scientific board for BioMarin, CSL Behring, Catalyst Biosciences, Novo Nordisk, Roche, Sanofi, Spark and Takeda; and has received speaker bureau fees from ISTH, Novo Nordisk, Pfizer, Roche, Sanofi, Takeda and WFH. W.M. reports consultancy and research funding for Bayer, BioMarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, SOBI, and Takeda. J.O. has received research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum, and Takeda; consultancy, speakers bureau, honoraria, scientific advisory board, and travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugai, CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda. M.R. his institution has received research funding from Bayer, BioMarin, CSL Behring, Genentech, Grifols, Hema Biologics, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, and uniQure; he has acted as a paid consultant to CSL Behring, Genentech, Hema Biologics, Novo Nordisk, Pfizer, Sanofi, Takeda, and uniQure; and he is on the board of directors of Partners in Bleeding Disorders. L.A.V. has no conflicts of interest to disclose. A.P.W. receives research funding from Octapharma, as well as honorarium for advisory board/consultancy from Bayer, BioMarin, CSL Behring, Genentech, Novo Nordisk, Octapharma, Pfizer, Sanofi, and Takeda. S.W.P has received grants/research support from Siemens and YewSavin and has served as a consultant to Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, Equilibra Bioscience, GeneVentiv, HEMA Biologics, Freeline, LFB, Novo Nordisk, Pfizer, Poseida Therapeutics, Regeneron/Intellia, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics, and uniQure.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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