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Current Practice in Management of Muscle Haematomas in Patients with Severe Haemophilia

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Key words : Muscle bleeding, muscle haematoma, diagnosis, physical examination, haemostatic intervention, physiotherapy

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Abstract

Muscle haematomas (MH) represent 10-25% of all bleeds in patients with severe Haemophilia. We performed a cross sectional survey on current practice in management of MH with participation from 22 consultants. The respondents reported 492 MH/year, corresponding an average of 25/centre, most associated with trauma. Iliopsoas (55%), calf (18%), and thigh (18%) bleeds were scored as most serious. Half of respondents distinguished between contusion and strains, whereas the majority (68.2%) did not categorise bleedings as intra- or intermuscular, although 77.3% routinely used ultrasound. Half of respondents used a standard protocol for management of MH. A total of 20 of 22 (90.9%) offered physiotherapy in the hospital following MH, with no clear consensus on timing and type of treatment. In a theoretical case, 70 kg patient with a soleus triceps haematoma, the average initial dose was 2730 U (range: 1750-4000) twice daily for 3-5 days. In a similar case of a patient with inhibitors, 31.8% reported first line and only use of either rFVIIa or aPCC, while 36.4% switched between bypassing agents. Using rFVIIa the median dose was 100 µg/kg (range: 85 - 270) and with aPCC the median dose was 70 U/kg (range: 50 - 100). The majority (68.2%) did not use antifibrinolytics. Resolution of pain (81.8% & 77.3%) was regarded the key clinical marker of arrest of bleeding as compared to diminished swelling and improved range of motion. The survey outlines limited consensus in management of MH in patients with Haemophilia and highlights potential topics for future studies.

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Introduction

Muscle bleedings in patients with Haemophilia often cause considerable pain and compromise overall physical capacity. Intramuscular haemorrhages are reported to represent approximately 10% -25% of all bleedings in patients with haemophilia [1]. In patients with severe Haemophilia, bleeds may become limb threatening. Recovery and rehabilitation may be protracted and insufficient. In contrast to spontaneous joint haemarthrosis, muscle bleeds are mostly associated with trauma [1]. In general, muscle haematomas in patients with haemophilia are often considered as difficult-to-treat bleeds. Insufficiently treated muscle bleeds may result in several complications such as e.g. irreversible damage to the muscles, including compartment syndrome, reduced range of motion, loss of function, myositis [2], damage to tendons (Volkman's ischemic contractures) [3], as well as excessive blood loss, infection, peripheral nerve complications, and development of haemophilia pseudo tumor [4]. Unfortunately, the majority of research and development within Haemophilia are focused on mechanisms related to preventing haemarthrosis and maintaining a good functional joint status. Only very few publications have reported on aspects of muscle haematoma in patients with severe Haemophilia [1;5]. Predominantly, reports have focused on management of m. psoas major bleeds [6;7] and haemophilia pseudo tumors [8-10]. As of today, limited consensus exists regarding choice of factor concentrate, dosages of factor substitution utilised, frequency of dosing, and duration of the haemostatic treatment. In particular, in patients with severe Haemophilia and inhibitors, studies supporting various approaches to treatment regimens do practically not exist. Finally, important information on concomitant and adjuvant treatment such as physiotherapy are rarely specified or described in detail.

The aim of the present study was to conduct a cross-sectional study on current practice in management of muscle bleeds in patients with severe Haemophilia A amongst haemophilia comprehensive care centres from UK, Denmark, Ireland, and Australia based on an electronic mail questionnaire.

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Materials and Methods

Definition and classification of a muscle haematoma

In the present study, a muscle haematoma was defined as a bleeding in any anatomical skeletal muscle group. Clinical classification and differentiation between different types of muscle haematoma are described in a recent review (ref).

Questionnaire on current practice of muscle haematoma

An electronic questionnaire was developed addressing evolvement of muscle haematoma, diagnosis of muscle haematomas, haemostatic intervention of muscle bleeds in patients with severe haemophilia without and with inhibitors, use of concomitant or adjuvant haemostatic intervention, diagnostic procedures, and physiotherapy (See Appendix 1). The questionnaire was emailed to consultant haematologists from 50 registered Haemophilia comprehensive care centres (CCC) in the United Kingdom (UK), Ireland (IR), Denmark (DK), and Australia (AUS). We advised that the questionnaire was answered by the consultant haematologist and not by junior doctors or nurses. Centres were asked to answer questions regarding adults only. Respondents reported estimated figures rather than actual measured data. Each participant was offered £100 for the effort and time spent filling out the questionnaire. All e-survey was circulated by June 2008. We allowed a period of 1 month for answering the questionnaire. Gentle reminders were emailed once a week. Following closure of the study period, results from the questionnaire were organized, analyzed and interpreted by the authors. In order to ensure the validity and quality of data, two of the investigators (RB and BS) independently listed the results in a preformed excel spreadsheet, using a predetermined checklist. In case of doubt or disagreement of the meaning of the responses, the third investigator (JI) evaluated the questionnaire.

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Data analysis and statistical considerations

Quantitative data and categorical data are presented using descriptive statistics. Qualitative statements are organized in tables, whereas quantitative measures are listed as figures and graphically illustrated.

Ethical considerations

The data from each participant are anonymous; hence, none of the results can be referred back to a specific centre. The questionnaire did not include specific patient data.

Results

Frequency and aetiology of muscle bleeding

In total 22 consultants representing 20 comprehensive haemophilia care centres in UK (17), IR (1), DK (2), and AUS (2) responded to the questionnaire. The respondents reported an estimated number of 492 muscle haematomas/year, corresponding an average of 25/CHCC. Using a score system ranging from 0-10 (0 representing *never*, 10 representing *always*) the aetiology of muscle haematomas was predominantly assessed as associated with trauma (score 7.1 of 10) rather than spontaneous development (4.0 of 10). Amongst a list of different anatomic localisations of muscle haematomas, Iliopsoas (55%), calf (18%), and thigh (18%) bleeds were scored as the most serious (Figure 1).

Diagnostic procedures

Half of the respondents stated they distinguish between contusion and strains, whereas the majority (68.2%) did not categorise bleedings as intra- or intermuscular, although 77.3% routinely used diagnostic ultrasound.

Haemostatic intervention

Only 50 % of respondents reported using a standard protocol for management of muscle haematomas.

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The questionnaire outlined a theoretical case: "An objectively verified muscle haematoma in the soleus triceps of a lower limb of a 29 year old patient, weighing 70 kilos with severe Haemophilia A." followed by questions addressing i) initial dosages of factor, ii) subsequent dosages of factor, iii) duration of therapy, iv) tapering of dosages or dose frequency, as well as v) addition of an anti-fibrinolytic.

Haemostatic intervention in patients with severe Haemophilia A without inhibitor

The average initial dose of factor VIII was 2730 U (range: 1750-4000). Treatment was continued for a mean of 3-5 days (range: 1-10). Subsequent dosages were similar to the initial dosage, although the majority of respondents indicated they were tapering the dosage and dose frequency based on daily assessment of each individual case. The majority (77.3%) of consultants did not distinguish recombinant factor VIII from plasma derived factor VIII concentrate containing von Willebrand factor. The total amount of factor VIII used ranged from minimum=4500 U to maximum=50000 U (median=10750 U, mean=17103 U) depending on the severity, type and anatomical localisation of the haematoma.

Haemostatic intervention in patients with severe Haemophilia A with inhibitors

In a similar case of a patient with inhibitors, 31.8% reported first line and only use of either recombinant factor VIIa (rFVIIa) or plasma derived activated prothrombin complex concentrate (pd-aPCC), while 36.4% switched between bypassing agents. Using rFVIIa the median starting dose was 100 µg/kg (range: 85 - 270) and with aPCC the median dose was 70 U/kg (range: 50 - 100). Subsequent dosages ranged from 85-270 µg/kg for rFVIIa (mean=110) and 50-75 U/kg (mean=63) for pd-aPCC. Dosing interval was 2-3 hrs for rFVIIa and 12-24 hrs for pd-aPCC. The average duration of treatment was 2.3 – 4.4 days, longer for pd-aPCC (4.1 days) than rFVIIa (2.8 days).

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For both patients with and without inhibitors, physicians generally expected haemostasis to be achievable within 6 hours, although up to 18% of centres allowed > 12 hrs to obtain haemostasis (Figure 2).

Adjuvant haemostatic intervention

The majority (68.2%) did not use concomitant antifibrinolytic treatment. The consultant reporting to use tranexamic acid, dosage regimens varied from 1g daily to 25mg/kg qds 6 hourly. The antifibrinolytic treatment was most often continued for 5-7 days.

Clinical marker of arrest of bleeding and maintaining haemostasis

Resolution of pain (patients without inhibitors: 18 out of 22 haemophilia treaters=81.8% & patients with inhibitors: 17 out of 22 haemophilia treaters=77.3%) was regarded the key clinical marker of arrest of bleeding and maintenance of haemostasis as compared to diminished swelling and improved range of motion. Figure 3, Panels A and B illustrates the scoring of importance (1 important to 4 less important) amongst patients without and with Haemophilia, showing that pain was scored as the most important marker.

Physiotherapy

A total of 20 of 22 (90.9%) offered physiotherapy in the hospital following muscle haematomas. As outlined in Table 1, there was limited consensus on timing and type of treatment. RICE-treatment (rest-ice-compression-elevation) was recommended in most centres. All centres offered therapeutic ultrasound in the hospital setting, although there was limited agreement on the optimal timing of the intervention.

Grading of importance of further research and studies in management of muscle haematoma in patients with Haemophilia

The overall importance of further research and studies in management of muscle haematomas scored 7 and 8 (out of 10) for haemophilia patients without and with inhibitors.

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Discussion

Muscle haematomas represent difficult to treat bleeds in patients with severe Haemophilia. Multiple anatomical targets and various trauma mechanisms complicate the clinical evaluation, diagnosis, treatment and rehabilitation. Currently, limited consensus exists on the comprehensive management of muscle haematomas in Haemophilia patients.

The present survey verified that the majority of muscle haematomas has a traumatic aetiology. It may be speculated whether patients with inhibitors are more prone to develop muscle haematomas than patients without inhibitors. Some studies suggest that muscle haematomas represent 10% of all bleeds in patients with severe Haemophilia [1]. However, the data from the US home treatment study of rFVIIa suggest that up to 23% of bleeds in patients with inhibitors are muscle haematoma [11]. These questions were not explored in further detail in the present study, however, should be kept in mind for future investigations.

Not surprisingly, iliopsoas muscle bleeds were reported as the most severe type of muscle haematoma. Likewise, the majority of previous reports and studies have focused on the iliopsoas bleeds [6;7].

The study revealed sparse consistency regarding diagnostic procedures. Only half of the respondents distinguished contusions from strains. The majority of centres listed the use of ultrasound for diagnosis. However, only few differentiated between intra- vs. inter-muscular localisation of the haematoma. Diagnostic classification of muscle haematomas is a complicated clinical discipline and in the current issue of Haemophilia we have reviewed classification and strategies for optimised diagnosis of muscle haematomas [12].

Moreover, the questionnaire highlighted limited agreement regarding dosing regimens and duration of the pharmacological therapy. Only half of respondents stated to have a specific written protocol on recommendations for coagulation factor treatment of muscle bleeds. Thus, the total amount of factor VIII used

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varied considerably. The lack of consensus was even more pronounced with Haemophilia patients with inhibitors. A potential explanation for the variation in treatment regimens could be the markers of arrest of bleeding and achieved haemostasis. The respondents of the survey predominantly used pain rather than reduced swelling and improved range of motion as the marker for arrest of bleeding as well as achieved haemostasis. It is noteworthy that, even in professional athletes the entire repair process and rehabilitation period following muscle injuries may take more than 30 days [13]. Pain may be considered a physiological response to muscle damage and present despite arrest of bleeding and normal haemostasis. Hence, it seems that optimised measures for assessing ongoing bleeding and achieved haemostasis are essential for optimising treatment regimens.

The majority of participants indicated a time period of less than 6 hrs as the preferred / accepted time to arrest of bleeding. There was a slight tendency to accept of longer time to arrest of bleeding in patients with inhibitors. This may be due to less predictability regarding haemostatic response as well as difficulties in monitoring and dosing the bypassing agents.

Recently investigations have shown that patients with severe Haemophilia not only suffer from compromised thrombin generation, but also insufficient clot stability caused by delayed and incomplete activation of FXIII [14] and increased susceptibility toward accelerated fibrinolysis [15]. Clinical studies have suggested a potent effect of concomitant antifibrinolytic treatment with tranexamic acid [15]. However, the majority of responders in the survey stated not to use adjuvant tranexamic acid for muscle haematoma. The study did not explore reasons for limited use of tranexamic acid. Lack of clinical studies may be one reason, whereas theoretical speculations on thrombotic risk may be another explanation. Further mechanistic as well as clinical studies would be desirable.

The timing and type of adjuvant physiotherapy recommended revealed considerable discrepancy. The RICE principle and therapeutic ultrasound was

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commonly recommended. However, a series of other interventions were mentioned and recommended. Obviously, it would be interesting to develop a series of systematic studies challenging various physiotherapy regimens. The current issue of Haemophilia lists some experiences from Sports Physiotherapy that may prove useful for improving overall rehabilitation and prevention of muscle injuries in patients with severe Haemophilia [12]. Recent publications have proposed a beneficial and potentially protective effect of regular exercise in patients with severe Haemophilia [16]. Optimized muscular function may protect against joint bleedings and improved fitness was associated with a higher rating of quality of life [17-19]. Likewise, a recent study describe a conservative and non-operative physiotherapeutic regime for the management of chronic haematomata and pseudotumors in patients suffering from haemophilia [20].

The study contains a series of important limitations. This cross sectional study only provides a random sample of current management of muscle haematomas. The nature of the study design does not provide valid data on causality, neither on actual measured frequencies and dose regimens. Respondents may have reported on their preferred/wished treatment modality, with no assurance that the data reflect actual practice. As an example, the numerous types of physiotherapy may reflect what consultant haematologists would like to offer, rather than what is actually available. The questionnaire was sent to 50 random comprehensive haemophilia care centres, however, only centres from UK, Ireland, DK, and Australia were enrolled. Thus, selection and information bias may be present and the data has reduced external validity.

In conclusion, the present survey suggests the need for further studies on the pathology, diagnosis, and importance of early treatment to achieve rapid control of bleeding, as well as rehabilitation following muscle haematomas in patients with Haemophilia. A prospective international multicentre registry of current management of muscle haematomas seems desirable to get more data. Optimised and systematic diagnosis may facilitate a better strategy regarding type and timing of physiotherapy.

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Acknowledgement

We are grateful to colleagues at comprehensive haemophilia care centres in UK, DK, Ireland, and Australia for their time and effort in responding to our questionnaire.

Appendix

A pdf-copy of the questionnaire can be obtained by emailing the corresponding author.

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Figures

Figure 1

Anatomical localisation of most severe muscle haematoma

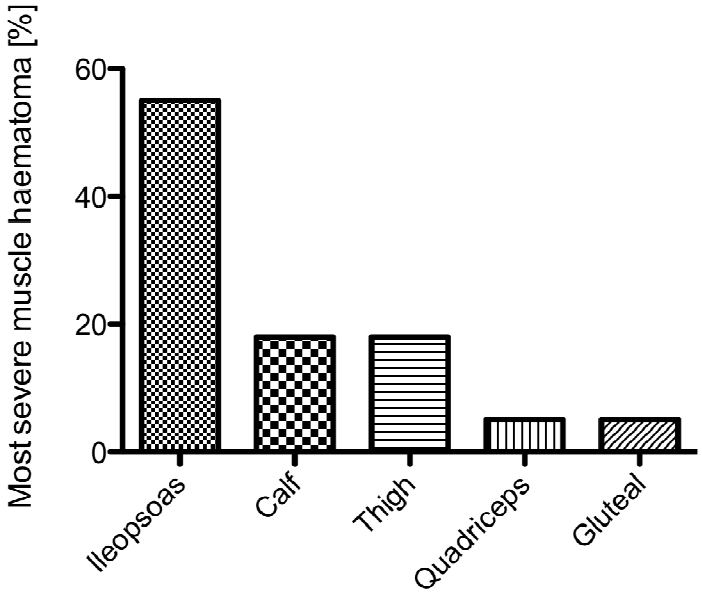

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Figure 2

Accepted time to arrest of bleeding

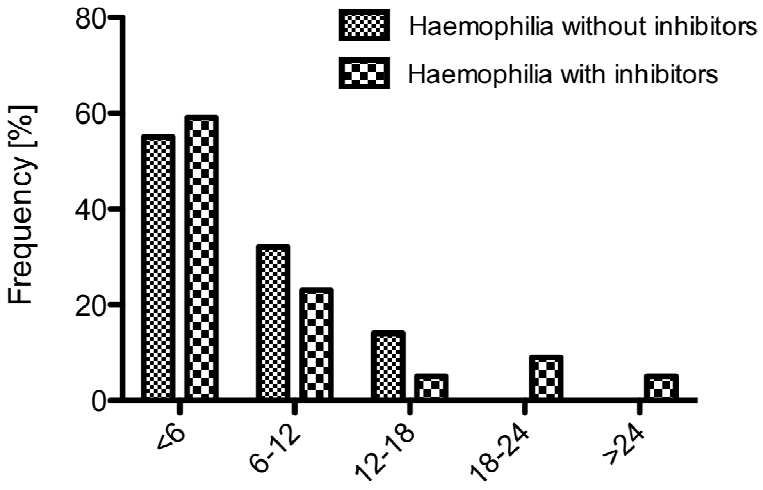

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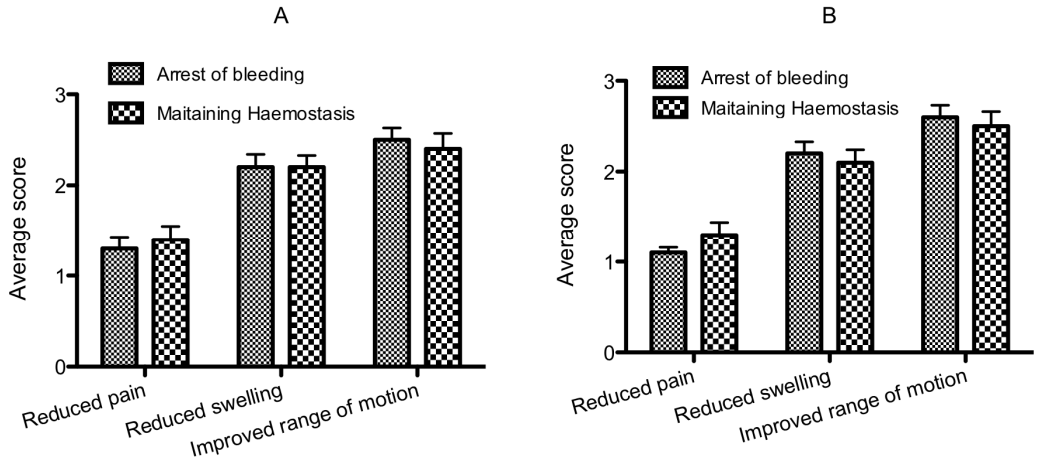
Figure 3

Markers of arrest of bleeding and maintaining haemostasis



Panel A: Haemophilia patients without inhibitors

Panel B: Haemophilia patients with inhibitors

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Legends

Figure 1

Anatomical localisation of most severe muscle haematoma

Illustrates frequency data (%) on the anatomical localisation of the most severe muscle haematoma.

Figure 2

Accepted time to arrest of bleeding

Depicts the accepted time to arrest of bleeding in patients without and with inhibitors.

Figure 3

Markers of arrest of bleeding and maintaining haemostasis

Illustrates the results of score of importance of the three clinical markers: reduced pain, reduced swelling, improved range of motion as defined by subjective reported relief of pain, reduced circumferential measure, and measurement of the achievable distance between the flexed position and the extended position of a particular muscle group, respectively. The score 1 corresponds most important, whereas the score 3 corresponds least important.

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Tables

Table 1

Timing and type of physiotherapy

	SUPER ACUTE PHASE (0-24 HOURS)	ACUTE PHASE (24-72 HOURS)	SUB ACUTE PHASE (4-21 DAYS)	POST ACUTE PHASE (>21 DAYS)
RICE	10/22 – 45.5%	9/22 – 40.9%	2/22 – 9.0%	1/22 – 4.5%
Megapulse Ultrasound	1/22 – 4.5%	2/22 – 9.0%	0	0
Passive movement	2/22 – 9.0%	2/22 – 9.0%	0	0
Walking aids	2/22 – 9.0%	3/22 – 13.6%	2/22 – 9.0%	4/22 – 18.2%
Mobilisation	0	2/22 – 9.0%	4/22 – 18.2%	3/22 – 13.6%
Isometric strengthening	0	2/22 – 9.0%	2/22 – 9.0%	0
Strengthening	0	0	2/22 – 9.0%	5/22 – 22.7%
Exercise	0	3/22 – 13.6%	3/22 – 13.6%	5/22 – 22.7%
Ultrasound	0	0	9/22 – 40.9%	2/22 – 9.0%
PSWD	0	2/22 – 9.0%	3/22 – 13.6%	0
Hydrotherapy	0	0	3/22 – 13.6%	1/22 – 4.5%
Active muscle contraction	0	0	1/22 – 4.5%	0
ROM exercise	0	1/22 – 4.5%	3/22 – 13.6%	2/22 – 9.0%
Massage	0	0	1/22 – 4.5%	0
Functional training	0	0	0	2/22 – 9.0%
Stretching	0	0	6/22 – 27.3%	4/22 – 18.2%
Re-assessment	0	0	0	3/22 – 13.6%
No intervention	10/22 – 45.5%	7/22 – 31.8%	4/22 – 18.2%	7/22 -31.8%

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Legends

Table 1

Timing and type of physiotherapy

Lists the recommended type of physiotherapy at various time intervals: 0-24hrs, 24-72hrs, 4-21 days, and >21 days. Data show number of responders as well as the frequency in percentages.

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