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Target Joint "New Concept of Identification"

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Abstract

Background: The hallmark of hemophilia is hemarthrosis. All efforts must be made to early diagnose joint bleeding as soon as it occurs and treat it not later than within 2 h of onset by infusing the appropriate clotting factor. This will prevent the accumulation of blood in the joint as well as inflammation and a potential hemophilic arthropathy. Recurrent bleeding prevents the joint from regaining its range of motion, muscle strength, and normal appearance. These changes become permanent, leading eventually to osteoarthritis. A bleeds joint requires urgent and comprehensive management, especially in young patients, if permanent damage is to be prevented.

Methods: The author conducted a comprehensive review and synthesis of the relevant literature. The author reviewed all compiled reports from computerized searches. Searches were limited to English language sources and human subjects. Literature citations were generally restricted to published manuscripts appearing in journals listed in Index Medicus and reflected literature published up to July, 2013. Results: The aim of this study was to introduce the new criteria (joint at risk) for early identification of "bleeds joint" for early diagnosis and effective management to prevent the joint to become chronic synovitis "target joint."

Conclusion: The new concept of identifying "target joint" in this study is aiming to prevent the joint of hemophilic patient to progress to stage of chronic synovitis "target joint" by early identification of bleeds joint.

Keywords: Arthropathy; Hemoarthrosis; Hemophilia; Prevention; Synovitis; Target joint

Introduction

Arthropathy is a major cause of morbidity in patients with hemophilia [1]. In the United States, 36% of patients with severe hemophilia tracked in the Centers for Disease Control and Prevention universal data collection database report the need for mobility assistance (cane, crutches, walker or wheelchair), and 30% miss school or work (mean of 7.5–11 days/year) due to upper or lower extremity joint problems [2]. Joint destruction is initiated by bleeding into the joint [3], a common site of hemophilic bleeds. In fact, it has been estimated that approximately 80% of bleeding episodes in patients with hemophilia occur in the muscles and joints [3,4]. While patients with severe hemophilia may experience spontaneous bleeding into joints, patients with milder forms of hemophilia typically experience joint bleeds in response to trauma [4]. Indeed, repeated joint bleeding is one of the distinguishing clinical characteristics of severe hemophilia [5].

Once blood enters the joint, a sequence of events is triggered that culminates in disabling arthropathy [5]. The inflammatory response induced by blood in the joint space causes the synovial tissue to become highly vascularized, making it susceptible to further bleeding. An endless loop develops in which joint bleeds are repeatedly followed by synovitis, which, in turn, leads to more hemarthroses [3,5]. Ultimately, destruction of the synovium causes fibrosis, breakdown of cartilage and arthropathy [4]. Clinical manifestations include joint swelling, pain, limitations in range of motion (ROM), muscular atrophy, and stiffness [4,5]. Joint damage can occur after only a few hemarthroses [6]. Under these conditions, the joint has become a "target joint." When the joint become a "target," the joint will initiate a destructive process, resulting from mechanical, chemical, and enzymatic mechanisms, which may result in irreversible damage. When the joint is beyond a certain level of articular damage, which varies among individuals, an osteoarthritic process becomes established, which progress independent of prophylaxis with factor will concentrate.

The correlation between a very low annual joint bleeding rate (AJBR) and the preservation of joint health in patients with severe hemophilia was reported by Nilsson *et al.* more than 20 years ago [7]. Among 20 young men aged 13–17, 17 of those (85%) with orthopedic and radiologic scores of 0/0 had an AJBR of just 0.1–1.4 (median: 0.3) after starting prophylaxis between ages 1 and 5. Similarly, a 6-year longitudinal study by Aledort et al. of orthopedic outcomes in 40 adolescents and young adults found that patients with pristine joints (i.e., an orthopedic/radiologic score of 0/0) had an average AJBR of 1.8 [8]. A retrospective chart review by van den Berg of 70 children followed-up for a mean of 15.6 years found that patients with an AJBR <3 had lower orthopedic joint scores than did those who bleed more frequently [9]. Likewise, in a prospective assessment of 24 joints (10 knees, 14 ankles) in 15 children and teenagers, Funk et al. found that three bleeding events into the same joint resulted in changes in orthopedic, radiologic, and magnetic resonance imaging scores and that ≥4 bleeding caused substantial joint damage [10]. In a comparison of intermediate-dose and high-dose prophylaxis conducted by Fischer et al., mean AJBR in 42 patients receiving intermediate-dose prophylaxis was 3.7, which was associated with a mean Pettersson score of 0 [11]. Yet only 54% of these individuals had a radiologic score of 0, as compared with all 18 patients whose mean AJBR was 0.2. In a study of 56 ankle joints in 38 boys with hemophilia conducted by Lundin *et al.,* the radiologic score was 0 for joints with <3 bleeding per joint and ≥1 for ankles with ≥3 bleeding per joint [12]. In addition, in an evaluation of 80 patients, van Dijk et al. reported that those with a Pettersson score of 0 had a median AJBR of 2.1 [13]. The association between deviations from normal joint ROM and bleeding frequency was evaluated in a cross-sectional evaluation of 4343 male patients with hemophilia aged 2–19 years treated at 136 US Hemophilia treatment Centers [14]. Among patients with severe hemophilia, the study showed a statistically significant difference in ROM scores associated with 0 hemarthroses in the previous 6 months as compared with either one to four joint bleeding or ≥ 5 joint bleeding episodes during this time period. Recently, Fischer *et al.* updated their experience with intermediate-dose and high-dose prophylaxis [15]. After more than 20 years of follow-up, 100% of patients in the high-dose (Swedish) cohort (n = 50; median age 23.2 years) had a median AJBR of zero (range: 0.0–2.0), and 89% had an orthopedic score <10. Overall, the group had significantly lower joint scores and fewer limitations in daily activities compared with the Dutch cohort, who experienced only slightly more hemarthroses (median AJBR 1.3; inter-quartile range 0.8–2.7). In addition, the need of orthopedic surgery was lower in the Swedish group (8%) versus the Dutch cohort (15%).

Not surprisingly, frequent bleeding also adversely affects health-related quality-of-life (HRQoL). During field-testing of the Haemo-QoL questionnaire in six Western European countries, children with an auditory brainstem response (ABR) <3 had significantly better scores in the dimensions of "view" (children aged 4–7 years), "friends" (children aged 8–12 years), "physical health" and "perceived support" and "sport" (patients aged 13–16 years) than did those who bled more frequently [16]. When children with hemophilia A participating in the randomized ESPRIT study were evaluated using the same instrument, those in the on demand group (median AJBR = 5.5) had more impairment in the dimension of "family," reporting that they felt overprotected by their parents, as compared with subjects receiving prophylaxis (median AJBR = 1.0) [17]. Adolescents and adults with hemophilia A enrolled in a paired comparison of on demand and prophylactic therapy who completed the short form-36 hQoL questionnaire at the end of each treatment period showed statistically significant improvements in "bodily pain" and the "physical component summary score" after prophylaxis (median ABR = 1.1) versus on-demand treatment (median ABR 43.9) [18]. In addition, among 470 children with severe haemophilia A from 10 countries evaluated using the PedsQL inventory, the total score was significantly better and similar to scores for the general pediatric population in children with an ABR ≤2 compared with those whose ABR was ≥3 [19]. Academic achievement is another HRQoL measure that is impacted by hemophilia-related bleeding. Shapiro et al. found that the number of bleeding episodes was positively correlated with school absenteeism, and that children with more school absences had lower scores in mathematics, reading and total achievement [20]. Although a comparable study has not been conducted in adults, it seems reasonable to assume that bleed-related absences from work may limit an individual's chances for advancement and professional fulfilment.

Kern *et al.* [21] studied 16 boys, over a 20-year period, in order to assess the financial impact of the development of a "target joint." These patients were managed similarly, both for treatment of a joint bleed (2 infusions/ bleed) and for management of persistent "target joint" bleeding (prophylaxis followed by surgical synovectomy). Fifteen of the patients developed a target joint, defined as 3 bleeds over a 3-month time frame. The results were not unexpected. The cost of treating a patient after development of a target joint increased by more than 2-fold, and the vast majority of this expenditure was related to factor concentrate (90%). The median age at which these children developed a target joint was just less than 4 years, with the youngest child being 15 months of age? These 15 patients developed an average of three target joints over the course of observation. The number of bleeding episodes after establishment of a target joint tripled from baseline (3 bleeds before target joint development; 10 bleeds after). Patients underwent surgery for persistent synovitis approximately 2 years after initiating prophylaxis. The conclusion from this study seems firm; that treatment of target joint bleeding is expensive. Yet the implications of these findings that prophylaxis is the best means to reduce target joint bleeding, may be less certain.

From above studies, we can see that the ideal management of bleeds joint from preventing him to progress to a target joint is to prevent its initial occurrence by early identification of bleeding, aggressive management and to reduce number of bleeding.

Identification of a Target Joint

As in the past the "target joint" identify as "a joint in which recurrent bleeding has occurred on four or more occasions during the

previous 6 months or one in which 20 lifetime bleeding episodes have occurred," [22] which unfortunately is a late Identification (diagnosis) of hemophilic arthropathy, but as today the ideal management of a bleed joint is to prevent its initial occurrence or to reduce the number of bleeding before to reach the stage of chronic synovitis "target joint," Which is the aim of this study to introduce the new sensitive valuable criteria know as Risk factors (joint at risk) which can be used by any hemophilia health care provider for early identifying the "target joint."

Criteria "joint at risks"

1- Pain at rest
- Microhemorrhage into the joints or subchondral bone causes deterioration of joints without clinical evidence of hemarthroses [23].

2- Soft-tissue swelling on (plan X-ray)
- Stage I of Arnold-Hilgartenr classification.

3- 2nd time bleeding (Two bleeds into the same joint within 2 months) [24].

4- Single massive bleeding.
- (Need aspiration) [25].

The new concept of identifying the "target joint" is any joint meet two or more of above criteria (Joint at risk) at any age or time will be defined as "target join."

Conclusion

It is much easier to prevent joint damage than to repair it after it has happened. In fact, once a joint is damaged, doctors may be able to slow down or stop additional damage, but they cannot make the joint like new. Strong evidence is now available that the most effective way to prevent joint damage in patients with hemophilia is early identification and reducing the incidence of joint bleeding–including bleeding that may be clinically undetectable–at an early age [23]. The new concept of identifying "target joint" in this study is aiming to prevent the joint of hemophilic patient to progress to the stage of chronic synovitis "target joint" by early identification of bleeds joint.

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