



Short communication

Successful perioperative management of three patients with hereditary angioedema without C1 esterase inhibitor therapy: A developing country perspective

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ARTICLE INFO

Keywords:

Androgens
Fresh frozen plasma
Hereditary angioedema
Stanozolol
Tranexamic acid

ABSTRACT

Background: Hereditary angioedema (HAE) is a rare inherited disorder characterized by sudden and unpredictable appearance of swelling. Surgical procedures, even minor ones, are known to precipitate an attack in these patients. C1 esterase inhibitor (C1-INH) therapy may be effective for short term prophylaxis in such situations. However, there is limited experience with short term prophylaxis in countries where C1-INH therapy is not available.

Methods: To report our experience of using short term prophylaxis for a dental procedure, a Cesarean section and a major hip surgery in one patient each with HAE in resource constrained settings.

Results: All 3 patients were given FFP before and during the procedure. While the first (a 6-year-old girl) and third patient (a 60-year-old male) were already taking stanozolol and the dose was doubled 5 days before the surgery, the second patient (28-year-old woman) was not taking any prophylaxis and she was initiated on stanozolol on the day of Cesarean section. The first patient was also given additional FFP one day after the dental procedure. After the procedure, the dose of stanozolol was decreased to baseline in patient 1 and 3 while it was discontinued in patient 3.

All 3 patients tolerated the procedures well and had no related episodes of angioedema.

Conclusions: Dental and other major surgical procedures in patients with HAE are known to precipitate an episode of angioedema. In countries where C1-INH therapy is not available, attenuated androgens and FFP may be used to prevent these episodes.

1. Introduction

Hereditary angioedema (HAE) is a rare inherited disorder characterized by sudden and unpredictable appearance of swelling. Surgical procedures, even minor ones, are known to precipitate an attack in these patients. C1 esterase inhibitor (C1-INH) therapy may be effective for short term prophylaxis in such situations (Busse et al., 2017; Zanichelli et al., 2020). However, when this therapy is either not available or not affordable, one has to take recourse to alternative measures with fresh frozen plasma (FFP) and attenuated androgens. We report 3 such cases

who were given short term prophylaxis with FFP and attenuated androgens, which successfully prevented procedure-related angioedema.

2. Case reports

2.1. Case 1

A 6-year-old girl was diagnosed to have HAE at the age of 3. Her father had had similar complaints since early childhood. Laboratory investigations revealed low C4 levels (0.04 g/L; Normal 0.16–0.48 g/L),

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<https://doi.org/10.1016/j.imbio.2020.152022>

Received 21 July 2020; Received in revised form 3 September 2020; Accepted 18 October 2020

Available online 3 November 2020

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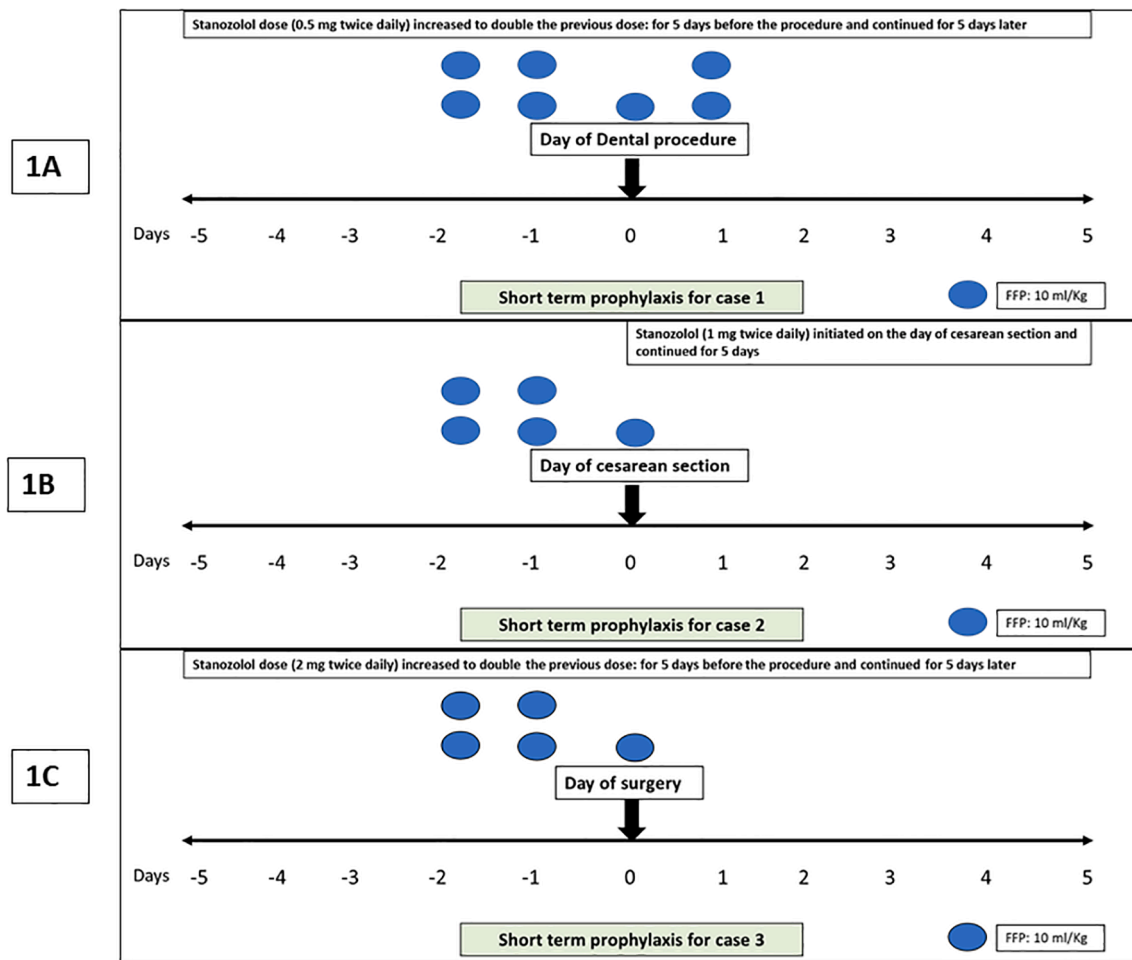


Fig. 1. Summary of short-term prophylaxis given in 3 cases 1A: Short term prophylaxis for a 6-year-old girl who underwent dental procedure (case 1) 1B: Short term prophylaxis for a 28-year-old woman who underwent Cesarean section (case 2) 1C: Short term prophylaxis for a 60-year-old male who underwent major hip surgery (case 3) Abbreviations: FFP: Fresh frozen plasma.

low C1-INH levels: 0.08 g/L (normal: 0.19–0.37) and low C1 inhibitor activity: 16.7% (normal: >68%). She was initiated on tranexamic acid (500 mg per day). However, because of inadequate response her therapy was switched to low dose stanozolol (0.5 mg per day). Her symptoms improved on this therapy. Attenuated androgens are not recommended for children and our patient had weight gain, hirsutism and early puberty attributed to this treatment (Maurer et al., 2018; Betschel et al., 2019; Gompels et al., 2005).

She presented to us at 6 years with a mandibular cyst that required excision. An attempt was made to procure plasma-derived C1-INH; however, parents could not afford the cost. The dose of stanozolol was increased to 0.5 mg twice daily and tranexamic acid was reinitiated (250 mg twice a day), 5 days before anticipated date of surgery. FFP infusion (10 ml/kg) was given prior to and during surgery (Fig. 1A). Excision of the mandibular cyst was carried out uneventfully under general anesthesia. She was extubated soon after surgery and the post-operative period was uneventful. She received 2 doses of FFP (10 ml/kg each) at 12 h intervals on the first post-operative day. Stanozolol and tranexamic acid were continued for 5 days and then gradually tapered (Fig. 1A). She remains well at 1-year follow-up while on stanozolol (0.5 mg alternate days) and tranexamic acid (500 mg three times a day).

2.2. Case 2

A 28-year-old woman was diagnosed with HAE at the age of 12. She had had episodes of acute abdominal pain and laryngeal edema. Her

paternal grandmother, father and younger sister had similar complaints. Laboratory investigations showed low C4 levels (<0.027 g/L; Normal 0.16–0.48 g/L) and low C1 inhibitor activity (31%). SERPING1 gene sequencing showed a splice site defect at exon 2-intron 2 junction (c.51+1G>A intron 2). She was initially managed with stanozolol (2 mg/day). However, because of side effects (weight gain, change in voice and hirsutism), she was put on tranexamic acid (1500 mg per day), and stanozolol was tapered and discontinued. She conceived uneventfully but had 2 spontaneous first trimester abortions while on tranexamic acid. She had no episodes of angioedema during either pregnancy. Tranexamic acid was discontinued and 6 months later, she conceived for the 3rd time. Her symptoms were much less marked during the 3rd pregnancy as compared with her non-pregnant state, and she experienced no major episodes of angioedema. An elective Cesarean section was planned at 38 weeks gestation under epidural anesthesia. FFP infusions (2 units) were given before and during surgery and stanozolol (2 mg per day) was initiated on day of procedure (Fig. 1B). She had no episodes of angioedema during surgery. The baby was successfully initiated on breast feeding on day 1. Stanozolol was discontinued after 5 days. Mother and baby remain well at 9 months of follow-up.

2.3. Case 3

A 60-year-old male was diagnosed to have HAE at the age of 29. However, he had been symptomatic since the age of 5 when he started developing recurrent episodes of swelling over face and hands along

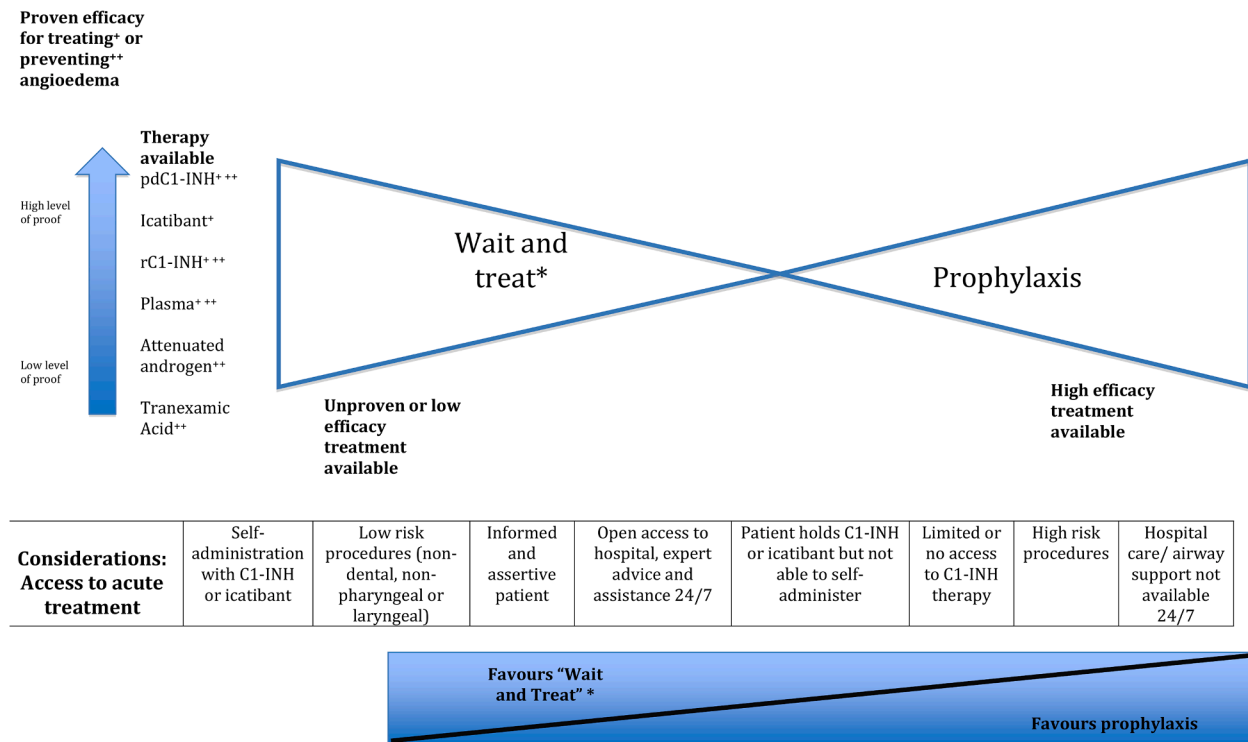


Fig. 2. Considerations for use of short-term prophylaxis Abbreviations: pdC1-INH: plasma-derived C1-INH, rC1-INH recombinant C1 inhibitor. * and treat if angioedema occurs.

with hoarseness of voice. His son, brother and 2 paternal cousins had had similar symptoms. Laboratory investigations showed low C4 (0.09 gm/l; Normal 0.16–0.48 g/L) and low C1INH levels (0.14 mg/L; N 3.02–4.14). Stanozolol (2 mg/day) was started and symptoms were partially controlled. However, he continued to have 4–5 mild episodes of angioedema per year.

At 60 years, he fractured the neck of his right femur and was advised to have open fixation. The dose of stanozolol was increased to 4 mg/day, 5 days before the date of anticipated surgery (Fig. 1C). He was also given FFP (2 units twice a day) for 2 days prior to surgery and 2 units during surgery. The surgery was carried out under spinal anesthesia and he tolerated the procedure well. The dose of stanozolol was decreased to 2 mg/day, 5 days after the procedure. He remains well at 1 month of follow-up.

3. Discussion

Episodes of angioedema in patients with HAE are unpredictable. However, an attack is often precipitated by surgical and dental procedures and may occasionally lead to life-threatening laryngeal edema (Hermans et al., 2012; Bork and Barnstedt, 2003). Up to 30% patients may develop an episode of angioedema after a surgical procedure in absence of prophylaxis (Aygören-Pürsün et al., 2013). Short term use of plasma derived C1-INH therapy has been recommended as the treatment of choice in these situations (Maurer et al., 2018; Longhurst and Bork, 2005; Valerieva et al., 2020; Grant et al., 2012). However, C1-INH therapy is not readily available in most developing countries and other options for short term prophylaxis are limited to androgens, tranexamic acid and FFP (Zanichelli et al., 2020; Tang et al., 2012; Williams and Craig, 2015; Farkas et al., 1999, 2012; Bork et al., 2011; Bowen et al., 2004). We herein report our experience of using short-term prophylaxis for a dental procedure, a Cesarean section and major hip surgery in patients with HAE in resource-constrained settings.

All 3 patients were given FFP before and during the procedure. While the first and third patients were already taking stanozolol and the dose

was doubled 5 days before the surgery, the second patient was not taking any prophylaxis. Stanozolol for long-term prophylaxis is contraindicated during pregnancy (Caballero et al., 2012; Czaller et al., 2010). However, older publications suggest that short term prophylaxis with attenuated androgens may be acceptable in the third trimester (Bowen et al., 2004). Vaginal delivery is preferred over Cesarean section and epidural anesthesia is considered safer than general anesthesia (Caballero et al., 2012; Czaller et al., 2010). Our patient underwent Cesarean section for obstetric indications. Stanozolol was initiated on the day of Cesarean section to minimise risk to the fetus.

Our prophylactic regimen was relatively intense (attenuated androgens and several doses of FFP) and guided by the availability of treatment coupled with concern about risk of angioedema. Current guidelines recommend C1-INH for short-term prophylaxis, with less costly options only where C1-INH is not available (Maurer et al., 2018; Farkas et al., 2012; Bowen et al., 2004; Ramaglia et al., 2019; Prematta et al., 2007). In particular, oral prophylactic agents are not recommended during pregnancy or breast-feeding (Maurer et al., 2018; Betschel et al., 2019). Current guidelines recommend against attenuated androgens for long-term prophylaxis in children and adolescents (Bowen et al., 2004). These guidelines are important to ensure resource availability in countries with insurance-backed or government-based healthcare but may not always result in the most appropriate use of resources for settings where high-cost drugs are not funded or where the cost is met by individual patients and their families. In these settings, the decision to use prophylaxis, rather than a “wait and treat” approach, involves an individual risk assessment, taking into account the procedure-related risk, the prior severity and frequency of the HAE attacks and the availability of acute treatment for HAE during the 4–72 h post procedure period, when there will be increased risk of attacks. The choice of agent is also important. Human plasma contains C1-INH at a concentration of 1 unit/ml plasma. Where a safe plasma supply is available, this may be an option, as in our cases. Although the evidence for efficacy of oral agents is confined to case series, these are widely available, easy to administer and are likely to be well tolerated in short-

term use. However, there is almost no information on the best dose, timing or duration (Farkas et al., 2012; Bowen et al., 2004; Gompels et al., 2005). Our proposals for risk assessment are shown in Fig. 2.

To conclude, dental and other major surgical procedures in patients with HAE are known to precipitate an episode of angioedema. In countries where C1-INH therapy is not available, attenuated androgens and FFP may be used to prevent these episodes (Bork et al., 2011; Farkas et al., 2012).

CRedit authorship contribution statement

Ankur Kumar Jindal: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Ankita Singh:** . **Gummadi Anjani:** Conceptualization, Methodology, Data curation, Writing - original draft. **Anit Kaur:** Investigation, Data curation, Writing - original draft. **Manojkumar Jaiswal:** Data curation, Writing - original draft, Visualization. **Seema Chopra:** Data curation, Writing - original draft, Visualization. **Uttam Saini:** Data curation, Writing - original draft, Visualization. **Shalvi Mahajan:** Data curation, Writing - original draft, Visualization. **Amit Rawat:** Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Surjit Singh:** Conceptualization, Methodology, Validation, Data curation, Writing - review & editing, Visualization, Supervision. **Hilary Longhurst:** Conceptualization, Methodology, Validation, Data curation, Writing - review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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