Supplementation of C1-esterase inhibitor concentrates for a patient suffering from hereditary angioedema undergoing complex open-heart surgery

Takeshi Saitoa,*, Osamu Namuraa, Takayuki Honmab, Jun-ichi Hayashia

aDivision of Thoracic and Cardiovascular Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata City 951-8510, Japan
bDivision of Anesthesiology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata City, Japan

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Abstract

Hereditary angioedema (HAE) is an autosomal dominantly inherited deficiency of C1-inhibitor, and it is an extremely rare condition. During surgery, oedema can be induced by a variety of stresses, and a high mortality rate has been reported. Since open-heart surgery involves cardiopulmonary bypass, the inflammatory response and complement activity are increased, meaning that an even greater risk can be anticipated. Perhaps for this reason, the only reports to date of cases of open-heart surgery have been cases of short-term cardiopulmonary bypass or off-pump coronary artery bypass grafting (CABG). We provide the first report of long-term cardiopulmonary bypass (longer than 5 h) for open-heart surgery in a patient with HAE that did not result in any postoperative decline in respiratory function, systemic oedema, laryngeal oedema or similar complications, and a favourable outcome was obtained.

Keywords: Hereditary angioedema; C1-inhibitor; Cardiopulmonary bypass

1. Introduction

Hereditary angioedema (HAE) is an inherited disorder that results from a deficiency of C1-inhibitor (C1INH). C1INH deficiency activates the kinin and fibrinolytic systems, with the resulting bradykinin production contributing to oedema [1]. Angioedema has been reported to have numerous triggers, including psychological stress and physical injury. Mortality due to episodic attacks occurring during surgery has been reported to be 15—33% [2]. Even normal surgery imposes substantial stress on patients, but the pump oxygenator indispensable to open-heart surgery further increases cytokine concentrations and promotes rapid complement activation due to contact between the blood and foreign substances, such as air and artificial devices [3]. Accordingly, long-term cardiopulmonary bypass in patients with HAE is a challenging, extremely high-risk operation, and intra-operative management is extremely important.

2. Case report

A 73-year-old man (height 168 cm, weight 61 kg) with severe mitral regurgitation, moderate tricuspid regurgitation and atrial fibrillation was referred for mitral valvuloplasty, tricuspid annuloplasty and maze operation. Two of his eight siblings had HAE. At 71 years of age he was hospitalised for abdominal pain. Computed tomography (CT) revealed circumferential oedematous stenosis of the small intestine. Complement component 3 (C3) was 92.8 mg dl\(^{-1}\) (normal range: 65—135 mg dl\(^{-1}\)), complement component 4 (C4) was 3.5 mg dl\(^{-1}\) (normal: 13—35 mg dl\(^{-1}\)) and functional active serum C1INH was <25% (normal: 70—130%); HAE was diagnosed. Furthermore, the patient reported that psychological stress increased his oedema. Angioedema was subsequently controlled with 300—600 mg day\(^{-1}\) of Danan, with no occurrences. Danan was given until the day before surgery; 1000 U of C1INH (Berinert P, CSL Behring Corp., King of Prussia, PA, USA) were administered on the evening before surgery and immediately prior to cardiopulmonary bypass. Mitral valvuloplasty, tricuspid annuloplasty and maze operation were then carried out. Pump oxygenation used a total priming volume of 800 ml (including sustainable haemofiltration) and was carried out at moderate hypothermia (32 °C), with antegrade blood cardioplegia for myocardial preserva-
administered Berinert P in 40 cases and estimated that the cardiopulmonary bypass and surgery were anticipated to these cases, surgery was of short duration. In the present surgery on HAE patients (approximately six cases), but in all report, cardiopulmonary bypass lasted 51 min. There have bypass, obtaining a favourable outcome [6]. In Alvarez’s (4.8—5.7 g dl$^{-1}$ was performed simultaneously, using 500 ml h$^{-1}$ of bicarbonated Ringer’s solution as replacement fluid. Total protein concentration during pump oxygenation averaged 5 g dl$^{-1}$ (4.8—5.7 g dl$^{-1}$), and functionally active serum C1INH was maintained at 66—79% (Table 1). Surgery lasted 9 h 20 min, cardiopulmonary bypass lasted 5 h 39 min and aortic cross-clamping lasted 4 h 24 min. After the patient returned to the intensive care unit (ICU), neither anasarca nor laryngeal oedema was observed, and postoperative gas exchange was good (FiO$_2$ 40% and PaO$_2$ 195 mmHg). The patient was extubated 2 h after ICU admission. Danan administration was restarted from postoperative day 1 to control the HAE state. The patient had no postoperative complication associated with HAE. The duration of ICU stay was 2 days postoperatively, and he was successfully discharged on postoperative day 20.

### 3. Discussion

Perioperative management for HAE during cardiac surgery has yet to be established. Furthermore, the minimum C1INH and functionally active serum C1INH levels during open-heart surgery in HAE patients are unknown. Tappeiner recommends that C1INH be at least 50% of normal levels in HAE patients for normal surgery [4]. However, in the previous report of open-heart surgery case using only androgen therapy, it has been impossible to maintain C1INH at 50% until the end of cardiopulmonary bypass [5].

There have also been reports recommending preoperative C1INH in addition to Danazol. Alvarez continued with androgen therapy until surgery, and by administering 1000 U of C1INH prior to anaesthesia induction, he maintained both C1INH and functionally active serum C1INH levels at ≥50% of normal values until the end of cardiopulmonary bypass, obtaining a favourable outcome [6]. In Alvarez’s report, cardiopulmonary bypass lasted 51 min. There have been a number of previous reports of successful open-heart surgery on HAE patients (approximately six cases), but in all these cases, surgery was of short duration. In the present case, surgery was more invasive and the durations of cardiopulmonary bypass and surgery were anticipated to be longer than in any previously reported cases. Martinez administered Berinert P in 40 cases and estimated that the median half-life of C1INH was 46.5 h in mild HAE and 31.75 h in severe HAE [7]. The half-life of C1INH TIM3 (product information, Baxter Healthcare Corp., Deerfield, IL, USA) is 18 h, though Alvarez used a different type of C1INH. Therefore, we considered the half-life of C1INH when deciding on the timing of its administration. Furthermore, since this patient had a history of psychological stress-induced attacks, C1INH was given the night before surgery, when psychological stress would be at its height, and before cardiopulmonary bypass, when surgical stress would be greatest.

Previous reports have described no special contrivances with regard to the cardiopulmonary bypass system. Haemodilution resulting from cardiopulmonary bypass has been reported to reduce C1INH concentrations to 30—50% [5], and many authors have reported that cardiopulmonary bypass increases the inflammatory response [3]. Thus, attempts to minimise the effect of cardiopulmonary bypass are extremely important in open-heart surgery on HAE patients. In the present case, a cardiopulmonary bypass circuit with low priming volume was used to reduce haemodilution and contact with foreign substances in artificial devices to minimise complement activity during surgery and maintain C1INH levels through the priming solution. Haemofiltration during cardiopulmonary bypass has been shown to effectively reduce bradykinins (molecular weight 1100 Da) and cytokines [8,9]. The molecular weight cut-off value of haemofilter CXHC11S (product information, Terumo Corp., Somerset, NJ, USA), which we used for our case, is 65 000 Da. We implemented the sustainable removal of cytokines and bradykinins without C1INH (molecular weight 105 000 Da) during cardiopulmonary bypass, the time of greatest stress during surgery, to alleviate oedema and minimise the effect of cardiopulmonary bypass. Whether high-cytokine plasma acts as a trigger for HAE attacks is unclear, but since cytokines are known to increase complement activity, they may also be regarded as effective in HAE. In addition, there is a possibility that the myocardium was protected from ischaemia and reperfusion damage due to a long aortic cross-clamp time by maintaining an adequate blood concentration of a C1-inhibitor and led to a satisfactory postoperative cardiac function [10].

As a result, at the end of cardiopulmonary bypass, functionally active serum C1INH was maintained at 79%, despite cardiopulmonary bypass lasting longer than 5 h. After the patient returned to the ICU, there was no noticeable anasarca or laryngeal oedema, and no reduction in respiratory function or thrombo-embolic symptoms were observed, enabling extubation after 2 h. Thus, favourable perioperative management was achieved.

Maintenance of the C1INH level during the perioperative period and its management during cardiopulmonary bypass are important for successful open-heart surgery requiring long-duration cardiopulmonary bypass in HAE patients.

### Table 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Comment</th>
<th>C1q (8.8—15.3 mg/dl)</th>
<th>C1INH activity (70—130%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:50</td>
<td>Pre-induction</td>
<td>12.2</td>
<td>70</td>
</tr>
<tr>
<td>9:10</td>
<td>Post-intubation</td>
<td>12.2</td>
<td>68</td>
</tr>
<tr>
<td>11:30</td>
<td>Bypass + 30 min</td>
<td>8.8</td>
<td>66</td>
</tr>
<tr>
<td>16:40</td>
<td>Post-bypass</td>
<td>10.3</td>
<td>79</td>
</tr>
<tr>
<td>20:20</td>
<td>Post-operation</td>
<td>9.2</td>
<td>75</td>
</tr>
<tr>
<td>22:00</td>
<td>Pre-extubation</td>
<td>9.0</td>
<td>66</td>
</tr>
</tbody>
</table>

Time, clock time on the day of operation; C1q, subcomponent of complement 1; C1INH, C1-inhibitor.

### References


