The significance of tranexamic acid in bleeding ulcers

Version 2

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ABSTRACT

Background Bleeding ulcer is a common condition, especially among the elderly population and effective treatment is desirable. Tranexamic acid has been successfully used for many bleeding conditions. Its importance for patients with bleeding ulcer in the upper GI tract, however, has been debated. The aim of this retrospective study was to provide an overview of the prescription of tranexamic acid (Cyklokapron) and to investigate if tranexamic acid has a positive effect on patients with active bleeding ulcer disease.

Method This retrospective cohort study was performed as a review of medical records on patients at the Surgery Department, at the University Hospital in Linköping. Patients with complete esophagogastroduodenoscopy and ulcer disease were included and grouped on the basis of treatment with tranexamic acid or not, among other treatments. Differences between the groups were statistically analyzed.

Results The main part of the prescription of Cyklokapron, 65%, occurred during 2010 and 2011, and 35% between 2012 and 2013 (p < 0.05). In the group treated with tranexamic acid, 84.3% needed blood transfusion, compared to 64.5% in the control group (p=0.039). Of the patients treated with tranexamic acid, 17.5% were re-bleeding compared to 13.6% of the controls (p=0.594). Median value for days at hospital was 5 in the tranexamic group and 3 in the control group (p=0.005).

Conclusion The prescription of Cyklokapron has declined between 2010 and 2013. The effect of tranexamic acid on active bleeding ulcer patients can not be concluded from this study. Further investigation is required to conclude the significance of tranexamic acid for patients with bleeding ulcer disease.

Keywords: Bleeding ulcer, Esophagogastroduodenoscopy, Hematemesis, H.pylori, Melena, Tranexamic acid
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>EGD</td>
<td>Esophagogastroduodenoscopy</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Hb</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>MAF</td>
<td>Microaggregate filter erythrocytes</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>p.o.</td>
<td>Per os</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Science</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>t-PA</td>
<td>Tissue plasminogen activator</td>
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<tr>
<td>TXA</td>
<td>Tranexamic acid</td>
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</table>
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INTRODUCTION

Upper gastrointestinal (GI) bleeding is a common and potentially fatal condition [1]. The bleeding derives from oesophagus, stomach or duodenum with Treitz ligament as division between the upper and lower GI tract. Gastric cancer, oesophagitis, Mallory Weiss’ tear and varicose veins are examples of different etiologies to bleeding conditions in the upper GI tract. Peptic ulcer from the stomach or duodenum is the most common cause of bleeding disease in the upper GI tract [2] and bleeding ulcer led to hospitalization for approximately 35 per 100,000 inhabitants in Sweden in 2005. Hospitalization for hemorrhagic ulcer declined between 1987 and 2005, while mortality from ulcer disease increased from 5% to 6%. This is probably a result of the older patient group, since the median age for ulcer disease is 76 years [1], which to a higher extent implies co-morbidity with other serious diseases. Approximately 80% of ulcer patients spontaneously stop bleeding [3]. Duodenal ulcer is more common among males [4], although the incidence is increasing among elder women [5]. Bleeding ulcers in the oesophagus can be drug-induced [6] and will together with bleeding ulcers in stomach and duodenum constitute the main focus in this study.

H. pylori- pathogenesis and pathophysiology

The bacterium Helicobacter pylori (H. pylori) is the most important etiologic factor to gastritis, which was proven by Warren and Marshall [7]. Numerous studies have confirmed its significance in the development of gastric and duodenal ulcers. H.pylori colonizes the human, gastric mucosa and generates gastritis, which might develop gastric and duodenal ulcers and occasionally even cancer through a series of metaplastic changes [8]. The bacterial virulence factors contribute to its pathogenicity and the Cag genes, in particular, have been proven to be important in the development of ulcer disease [9]. As a result of a declining prevalence of H. pylori, hospitalization due to peptic ulcer has decreased in some Western countries [3, 10]. Immigrants in Western countries, however, present a higher prevalence of H. pylori infections. Socioeconomy also influences the risk of getting infected [11].

Except from H. pylori, additional factors are important in the development of peptic ulcer. Nonsteroidal anti-inflammatory drugs (NSAID) and Acetylsalicylic acid (ASA) contribute to the risk of developing peptic ulcer [12] due to their impairing activity on the gastric mucosa, which is normally an important defense protecting the stomach [13]. Selective serotonin reuptake inhibitors (SSRI) have a slight negative impact on the platelets and their clotting action, which is why this medication also might contribute to a disadvantageous coagulation
process [14]. Anticoagulant medication, smoking, alcohol and previous ulcer disease [12] are other factors increasing the risk for bleeding ulcer.

When the gastric mucosa is damaged and an ulcer is clinically significant, the condition is clinically manifested as hematemesis and/or melena, the cardinal symptoms of bleeding ulcer. The condition is more seldom presented as haematochezia, since fresh blood rather indicates that the bleeding source is located in the aboral part of the GI tract [3]. The gastric environment is acidic due to acid producing parietal cells in the gastric mucosa [13]. Low pH contributes to diminished platelet action and a disadvantageous environment for coagulation factors [15]. Pepsin is a factor additionally contributing to the anticoagulant action in the stomach [16].

_Treatments_

By means of esophagogastroduodenoscopy (EGD), the feature and expansion of the ulcer can be estimated, and depending on its appearance, the bleeding ulcer can be distributed according to the Forrest classification [17]. The essence when treating patients suffering from bleeding ulcer is to stop the bleeding and prevent further bleeding. Endoscopic treatment, implying injections such as adrenaline and thermal methods [18], is the state of art recommendation to treat the bleeding ulcer. If the methods previously mentioned are not satisfactory, surgery is possible. Endoscopic treatment is, however, today the most common way to treat bleeding patients due to the development of endoscopic techniques [19]. In addition, medical treatment comprises proton pump inhibitors [20] and therapies eradicating _H. pylori_, to prevent re-ulcer in the future [21].

_Tr'anexamic acid and fibrinolysis_

When coagulation has started, the fibrinclots are eventually degraded through fibrinolysis, which is important to maintain haemostasis and prevent occlusion. Urokinase and tissue plasminogen activator (t-PA) are responsible for the conversion of plasminogen to plasmin, which breaks down fibrin [22]. Medical treatment of peptic ulcer sometimes implicates tranexamic acid (TXA), which is a synthetic agent with antifibrinolytic effects due to its inhibiting action on plasminogen by inhibiting its lysine binding sites [23]. Cyklokapron, which is the name of the medical product, is consequently an antifibrinolytic medication and has been successfully used in different clinical trials [24-27].
The CRASH -2 trial included in total 20 211 trauma patients from 40 countries. In this randomized study it was concluded that TXA decreased the bleeding mortality from 5.7% in the placebo group, to 4.9% in the TXA group [24]. Furthermore, TXA medication seems to have a positive impact on patients going through radical retropubic prostatectomy [25], as well as it reduces the need of blood transfusion in hip fracture surgery [26]. Moreover, TXA reduces blood loss during menstruation implicating that it has an effect on the fibrinolytic process in the uterus, which is important for women suffering from menorrhagia [27]. Staël von Holstein et al. suggested that TXA could be a favorable complement when treating bleeding conditions in the upper GI tract [28].

The use of Cyklokapron for upper GI bleeding, however, has been debated during the last years. The medication was excluded from the Swedish State of the art recommendation, after the publication of a Meta analysis from The Swedish Council on Health Technology Assessment (May 2011) [29]. The authors indicated that there is not enough material to state its significance as inhibitor of fibrinolysis in the context of upper GI bleeding. The conclusion was based on a systematic review performed by Gluud et al., which included studies investigating the importance of TXA as a medical treatment to patients with upper GI bleeding [30]. In some trials, patients did not go through EGD examination [31] and the mean age in the trials was lower than what is generally considered for patients with upper GI bleeding. The analysis of previous studies investigating TXA as part of the medical treatment for upper GI bleeding, consequently resulted in the conclusion that there is not yet sufficient background to appoint it as an evident part of the treating program.

AIM

The aim of this study was to comprise the first part of a study that will provide an overview of the prescription of Cyklokapron in a Swedish University Hospital before and after the publication of the Meta analysis from The Swedish Council on Health Technology Assessment (2011), and further investigate if TXA can be beneficial as a part of the treating program for patients suffering from bleeding ulcer disease.
MATERIAL AND METHODS

Ethical consideration

This retrospective cohort study was performed during spring 2014 and in accordance with the ethical declaration from the updated Helsinki Declaration. Information about each patient was collected from medical records at the University Hospital of Linköping in Östergötland, Sweden. The study brought about some ethical aspects that had to be taken into consideration, since it was primarily a register study based on reviews of medical records, which contain information classified as confidential. The management of the medical records was performed with discretion and all included patients were unidentified. The study was performed with approval from the local ethical committee.

Study population

Initially, the symptoms and diagnoses connected to upper GI bleeding were gathered in form of diagnoses from International Statistical Classification of Diseases and Related Health Problems (ICD 10). Hematemesis (K92.0), melena (K91.1) and unspecified GI hemorrhage (K92.2) were the current diagnoses in the study. At baseline, all patients (men and women) diagnosed with melena, hematemesis and/or as unspecified GI hemorrhage at the acute surgical ward between 2010 and 2013, were registered. A secretary using the ICD coding system in clinical routine performed this process to find the current patients in the medical record system. Among these, patients suffering from both upper and lower GI hemorrhage were represented. EGD and ulcer disease, including oesophageal, gastric and duodenal ulcers, were the inclusion criteria. Through a review of the medical records (N= 597), patients who had not been examined through EGD and patients with no bleeding source in the upper GI tract were excluded (N=444). In 315 of these medical care events, no bleeding source was found in the upper GI tract during EGD, which included patients without a definite bleeding source and patients who had further been diagnosed with lower GI problems. Some patients were diagnosed with K92 diagnoses at different occasions and in these situations, each medical care event was calculated separately. Among the remaining individuals (N=149), the patients were grouped based on the cause of the bleeding. Patients with ulcer disease were finally included (N=101). The records of the included individuals were examined in detail on the basis of the date of arrival to the Surgery Department. The number of individuals treated and not treated with TXA was registered. Figure 1 presents in detail the number of the patients excluded and included, plus the specific reason for exclusion and inclusion.
Figure 1. Flow chart presenting number of medical care events excluded and included among patients diagnosed with K92 diagnoses at the Surgery Department, together with the specific reason for inclusion and exclusion.

The included patients received a number based on the order they appeared in the unidentified register. Even here, each hospital care event was calculated regardless of if the patient had been treated more than once, except from when the new medical care event occurred within
30 days after discharge, which in these situations was interpreted as re-bleeding. Though, patients that re-emerged with bleeding symptoms received the same number as the first time they were treated for ulcer disease. In case of uncertainty concerning the classification of a patient during the whole exclusion and inclusion process, the specific case was analyzed together with an experienced surgery. A specialized doctor, who afterwards dictated the normal/pathologic findings and diagnosed the patient, performed EGD.

**Study protocol**

Information about the patients was registered in a file based on a protocol framed to include medical history, treatment and outcome. The results from the review of the medical records were registered in the form of numbers corresponding to specific answers, 1 for yes and 0 for no. Missing values were also registered. The medical history was primarily found in time of registration at the emergency or surgery unit and included: gender, age, hematemesis, melena, abdominal pain or discomfort, systolic blood pressure, pulse, hemoglobin (Hb), smoking—and alcohol habits, previous diseases organized into different categories (cancer disease, cardiovascular disease, lung disease, diseases related to the kidneys and urinary tract, blood disease, joint disease, diabetes, infectious disease and other diseases). Medical history also included present medication comprising a risk for ulcer disease (NSAID, ASA, anticoagulant medication, SSRI) and risk medication administered within two months before the bleeding episode.

Medical treatment referred primarily to Cyklokapron medication of any kind, eradicative treatment (Nexium® HP) and proton pump inhibitors (PPI) during and/or after the medical care event (PPI i.v. or p.o. 20mg/40mg x 1 or 2). EGD examination within 24 hours, adrenaline injection alone or in combination with other endoscopic treatments (thermal/mechanical methods) and surgery were other treatments that were registered. The primary outcome factors were: re-bleeding within 30 days, defined as signs of a new bleeding episode, for example increase of melena or a sudden decline in Hb, re-gastroscopy, number of days hospitalized at the Surgery Department and/or at the Intensive care unit (ICU), death within 30 days after the medical care event (all-cause mortality) and the need of blood transfusion expressed as one or more microaggregate filter erythrocytes (MAF).

**Statistical processing**

Patients treated with and without Cyklokapron formed two separate groups. Mean age and distribution by gender were calculated for each group as well as mean value for blood
pressure, hemoglobin and pulse. Median value was calculated for the number of risk medications. Symptoms, previous/present diseases and outcomes were expressed as percent in each group. Median value was calculated for the number of days at the Surgery Department and/or at the ICU. Differences between the groups were statistically examined through the Chi-squared test and the Mann Whitney U test. All statistical calculations were performed in SPSS (Statistical Package for the Social Science). Missing values were registered and calculated in accordance with the statistical program. P-value < 0.05* was considered as statistically significant.
RESULTS

Medical history

Among the 597 medical care events where the ICD codes for melena, hematemesis and/or unspecified GI bleeding had been registered at the Surgery Department between 2010 and 2013, 101 admissions were registered as ulcer conditions. Cyklokapron was prescribed in 56% of the medical care events, whereas no Cyklokapron medication was prescribed in 44% of the cases. 65% of the Cyklokapron medication was prescribed during 2010 and 2011 and 35% was prescribed during 2012 and 2013 (p< 0, 05). Figure 2 gives an overview of the number of patients receiving Cyklokapron between the 4 years that have been investigated.

![Figure 2](image)

**Figure 2.** Trend in prescription of Cyklokapron between 2010 and 2013 expressed as numbers treated with TXA (serie 1) and without TXA (serie 2) of 101 medical care events in total.

Distribution by gender and mean age together with medical condition and cardinal symptoms for the included patients, are presented in total and for the groups treated with and without TXA (table 1).
**Table 1.** Mean value for age, systolic blood pressure, Hb and pulse together with confidence interval and distribution by gender, cardinal symptoms and abdominal pain expressed as number of patients of total number and as percent, in total and for each group separately.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Cyklokapron</th>
<th>No Cyklokapron</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women N/total N (%)</strong></td>
<td>45/101 (44.6)</td>
<td>24/57 (42.1)</td>
<td>21/44 (47.7)</td>
</tr>
<tr>
<td><strong>Men N/total N (%)</strong></td>
<td>56/101 (55.4)</td>
<td>33/57 (57.9)</td>
<td>23/44 (52.3)</td>
</tr>
<tr>
<td><strong>Mean age, years (CI)</strong></td>
<td>71 (CI 69-75)</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td><strong>Mean Systolic Blood pressure, mmHg (CI)</strong></td>
<td>121 (CI 115-127)</td>
<td>119</td>
<td>123</td>
</tr>
<tr>
<td><strong>Hb Mean value (CI)</strong></td>
<td>98 (CI 92-103)</td>
<td>93</td>
<td>102</td>
</tr>
<tr>
<td><strong>Pulse Mean value (CI)</strong></td>
<td>87 (CI 84-92)</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td><strong>Haematemesis N/total N (%)</strong></td>
<td>50/96 (52.1)</td>
<td>32/53 (60.4)</td>
<td>18/43 (41.9)</td>
</tr>
<tr>
<td><strong>Melena N/total N (%)</strong></td>
<td>75/96 (78.1)</td>
<td>42/53 (79.2)</td>
<td>33/43 (76.7)</td>
</tr>
<tr>
<td><strong>Haematochezia N/total N (%)</strong></td>
<td>11/91 (12.1)</td>
<td>7/49 (14.3)</td>
<td>4/42 (9.5)</td>
</tr>
<tr>
<td><strong>Abdominal pain or discomfort N/total N (%)</strong></td>
<td>40/93 (43.0)</td>
<td>19/50 (38.0)</td>
<td>21/43 (48.8)</td>
</tr>
</tbody>
</table>
In total, three patients had passed gastric bypass surgeries and 14 had experienced previous ulcer disease. The majority of the patients (97%) suffered/had suffered from one or several other diseases except from the present ulcer disease: cardiovascular disease (N=69), diabetes (N=23), cancer disease (N=18), disease in the kidneys or urinary tract (N=11), blood disease (N=8), joint disease (N=8), infectious disease (N=7), lung disease (N=6), parathyroid/thyroid disease (N=3) and other diseases (N=50). Results that concern medical history including previous and present cardiovascular disease and medication are compiled for each TXA group separately (table 2).

**Table 2.** Medical history in each group including: cardiovascular disease expressed as number of patients of total number, and as percent, together with median, maximum and minimum values for number of medications comprising a risk for ulcer disease, together with p-values.

<table>
<thead>
<tr>
<th></th>
<th>Cyklokapron</th>
<th>No Cyklokapron</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular disease N/total N (%)</strong></td>
<td>40/57 (70.2)</td>
<td>28/44 (63.6)</td>
<td>p=0.487 (Chi2-test)</td>
</tr>
<tr>
<td><strong>Number of medications comprising a risk for ulcer disease</strong></td>
<td>1 (0-4)</td>
<td>1 (0-3)</td>
<td>p=0.732 (Mann Whitney U test)</td>
</tr>
<tr>
<td><strong>Median value (min-max)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Treatment**

In total, 100% were treated with PPI during and/or after their hospitalization episode. 53 patients received a prescription of eradicative treatment (Nexium® HP), 28 received adrenaline injections during EGD, three went through surgical treatment (duodenotomy) and 21 patients were treated with other methods, including thermal and mechanical methods. The corresponding results for each TXA group are presented in table 3.

**Table 3.** Treatment and EGD within 24 hours for each group separately, expressed as number of patients of total number registered, and as percent, together with p-values.

<table>
<thead>
<tr>
<th></th>
<th>Cyklokapron</th>
<th>No Cyklokapron</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI N/total N (%)</td>
<td>57/57 (100)</td>
<td>44/44 (100)</td>
<td>No statistics are computed because PPI was a constant</td>
</tr>
<tr>
<td>Adrenaline N/total N (%)</td>
<td>20/55 (36.4)</td>
<td>8/43 (18.6)</td>
<td>p=0.053</td>
</tr>
<tr>
<td>Other treatments N/total N (%)</td>
<td>16/57 (28.1)</td>
<td>5/42 (11.9)</td>
<td>p=0.052</td>
</tr>
<tr>
<td>HP Eradication (Nexium ® HP) N/total N (%)</td>
<td>26/56 (46.4)</td>
<td>27/44 (61.4)</td>
<td>p=0.137</td>
</tr>
<tr>
<td>EGD within 24 hours N/total N (%)</td>
<td>47/57 (82.5)</td>
<td>31/44 (70.5)</td>
<td>p=0.154</td>
</tr>
</tbody>
</table>
Outcome

Signs of re-bleeding were registered in 16 of the medical care events and 63 needed one or more MAF. Medical care events at the Surgery Department solely occurred in 84 of the cases, whereas 17 occurred at the Surgery Department and at the ICU. The outcome results for each group are presented separately (table 4). Distribution by gender and median age for each outcome are presented in table 5. Three patients died within 30 days after the admission.

Table 4. Outcome factors for each group including MAF, re-bleeding, treatment at the Surgery Department and/or ICU, expressed as number of patients of total number and as percent, and median, maximum and minimum values for days at hospital, together with p-values.

<table>
<thead>
<tr>
<th></th>
<th>≥1 MAF N/total N (%)</th>
<th>Re-bleeding N/total N (%)</th>
<th>Days at hospital Median value (min-max)</th>
<th>Treatment at Surgery Department N/total N (%)</th>
<th>Treatment at surgery care unit and ICU N/total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyklokapron</td>
<td>43/51 (84.3)</td>
<td>10/57 (17.5)</td>
<td>5 (1-15)</td>
<td>43/57 (75.4)</td>
<td>14/57 (24.6)</td>
</tr>
<tr>
<td>No Cyklokapron</td>
<td>20/31 (64.5)</td>
<td>6/44 (13.6)</td>
<td>3 (0-39)</td>
<td>41/44 (93.2)</td>
<td>3/44 (6.8)</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.039* (Chi2-test)</td>
<td>p=0.594 (Chi2-test)</td>
<td>p=0.005* (Mann Whitney U test)</td>
<td>p=0.018* (Chi2-test)</td>
<td>p=0.018* (Chi2-test)</td>
</tr>
</tbody>
</table>
Table 5. Distribution by gender expressed as number of patients of total number and as percent, together with median, maximum and minimum age for the outcomes: MAF, rebleeding and treatment ward.

<table>
<thead>
<tr>
<th></th>
<th>MAF</th>
<th>Rebleeding</th>
<th>Treatment at the Surgery Department</th>
<th>Treatment at Surgery Department and ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men N/total</strong></td>
<td>37/56 (66.1)</td>
<td>10/56 (17.9)</td>
<td>46/56 (82.1)</td>
<td>10/56 (17.9)</td>
</tr>
<tr>
<td><strong>Women N/total</strong></td>
<td>26/45 (57.8)</td>
<td>6/45 (13.3)</td>
<td>38/45 (84.4)</td>
<td>7/45 (15.6)</td>
</tr>
<tr>
<td><strong>Age median value (min-max)</strong></td>
<td>76 (38-94)</td>
<td>74 (24-90)</td>
<td>73 (24-94)</td>
<td>75 (49-90)</td>
</tr>
</tbody>
</table>
DISCUSSION

The aim of this retrospective study was to provide an overview of the trend in Cyklokapron prescription before and after the publication of the Meta analysis from The Swedish Council on Health Technology Assessment in 2011, and to examine if treatment with TXA is favorable for patients with bleeding ulcer disease. A strength with this retrospective study is that all patients had passed EGD and were diagnosed with ulcer disease before they were included, which accordingly was an insurance of the etiology of the bleeding. Focusing the study on this specific condition made it clear that etiology and treatment were similar between the patients. The distribution by gender, women 45% and men 55%, respectively, was in accordance with previous incidence studies concluding that men suffer from ulcer disease more frequently than women [4]. The mean age was ≥69 in both groups, which reflects the generally accepted, high, mean age for bleeding ulcer patients.

The time when Cyklokapron was administered has not been taken into consideration since it, based on clinical praxis, is generally prescribed at the Emergency Department or when the patient arrives to the Surgery Department. An advantage with the exploration of Cyklokapron is that it is administered under controlled circumstances, which is why lack of compliance does not become a significant weakness in this study.

Only three of the included patients died within 30 days which is the reason that no statistical comparison could be performed between the groups with regard to this outcome. A slight difference was found between the two groups concerning re-bleeding, (17.5% in the TXA group and 13.6% in the group not treated with TXA, table 4). The result was not statistically significant, which can probably be explained as a consequence of the limited size of the patient group. Unlike the present study, Staël von Holstein et al. observed a lower frequency of re-bleeding in a group treated with TXA (N=10), compared to the placebo group (N=19). However, this result was neither statistically significant (0.097) [27].

Unexpectedly, the need of blood transfusion was greater among the patients who received Cyklokapron, than among patients not treated with TXA, in the present study. However, there were some missing values in this category as it appears in table 4. The present result is not in accordance with previous trials concluding that TXA in combination with acid reducing treatment will decrease the need of blood transfusion. Staël von Holstein et al. noticed that the mean number of blood transfusions was only 2 x 2 units in the group treated with TXA, compared to 3 x 2 units in the placebo group (p=0.018) [27]. Furthermore, time hospitalized
surprisingly appeared to be longer for patients in the TXA group compared to the control group, in the present study.

Table 2, however, presents a higher prevalence of cardiovascular diseases in the TXA group, which might be a significant confounding factor explicating the results. Moreover, patients in the TXA group needed adrenaline and other treatments more frequently than patients without TXA treatment, (p=0.053 and p=0.052, table 3). All together, these observations might be important since they signal that the patients in the TXA group were probably in a worse condition if compared to the patients that were not treated with TXA. The present results might consequently have been generated on the basis of a higher co-morbidity in the TXA group. The mean age was 4 years higher in the group treated with Cyklokapron, which might also be an important factor explaining why the patients in the Cyklokapron group were in a worse condition. Rockall et al. concluded that age and comorbidity are important factors determining the course of the bleeding ulcer disease [2].

This study shows that the main part, 65 %, of the TXA medication was prescribed during 2010 and 2011 compared to 35% between 2012 and 2013 (p<0.05). This was in accordance with the initial hypothesis that most of the Cyklokapron prescription would occur during 2010 and 2011, (before the publication of the Meta analysis from The Swedish Council on Health Technology Assessment in May 2011). It might take time for prescription recommendations to reach every clinician, which is why some prescription of Cyklokapron was expected after 2011. Nevertheless, the divergence in the prescription of Cyklokapron does signal that there might be a difference not only based on clinical routines, but even differences between individual clinicians in their prescription habits. Variations in the severity of a patient’s condition might influence if a clinician chooses to treat the patient with TXA or not. For this reason, an important confounding factor might be that patients in a more serious condition perhaps received the medication, while patients in a better condition did not receive TXA. Individual differences in prescription patterns among clinicians, based on variations in the patient conditions, are therefore a possible explanation to the current results. Based on this study, the prevailing theoretical insecurity about TXA and its significance for patients with bleeding ulcer disease, appears to be reflected even in the clinic.

One of the patients was treated at the Surgery Department for bleeding ulcer but was afterwards treated for serious co-morbidity at the ICU which is why many days at hospital were registered on this patient. Another patient re-emerged with upper GI bleeding but it was unclear if it was ulcer or varicous veins that had re-bled. For one patient it was not clear if the
bleeding had stopped completely between the bleeding episodes. Some of the patients differed from the rest concerning previous GI surgeries (N=3). (Patients who have gone through gastric bypass do not present a normal physiology due to the absence of the acidic environment.) For these reasons, these patients might have acted as disturbing elements in the present calculation.

Information about how the acidic environment influences the effect of TXA is crucial knowledge important to emphasize. Patchett and O’Donoghue examined the effect of gastric juice, in combination with TXA and other medications, on coagulation and fibrinolysis through thrombelastography, and concluded that TXA might have an effect on fibrinolysis in the presence of gastric acid, but not on coagulation [15]. Staël von Holstein et al. concluded in a double blind study that TXA could be fortunate for bleeding ulcer patients as a complement to acid reducing medication [27]. Medication reducing the acidic environment in the stomach might therefore be a prerequisite to receive a desirable effect of TXA. All patients received acid reducing medicine in the present study, which was an important observation due to its significance in ulcer treatment and the fact that it ascertained a similarity between the groups on this specific point.

The socioeconomic aspect is important to emphasize due to its essential role as a risk factor for ulcer disease. Staat et al. claimed that the level of education is affecting the risk of getting infected and concluded that *H. pylori* is common in groups with low socioeconomic status [11]. Compliance, uppermost referring to administration of medication that will prevent new bleeding episodes, might also depend on the socioeconomic status. Our intention was to include smoking- and alcohol habits in the calculation since they are both direct risk factors for upper GI bleeding, as well as they indirectly signal about socioeconomic conditions. Information about smoking and alcohol habits in medical records was, however, brief in general, which is why calculations on these factors were not completed. Information was not clearly registered in the majority of the cases, which would have generated a misleading result if it had been included. Nevertheless, smoking and alcohol habits are important factors to take into consideration when further studies are performed on the same subject.

In the clinic, the correct ICD code is not always connected to a specific condition, and the fact that information about patients is occasionally not registered in medical records, might be a problem from a research perspective. Åhsberg et al. appointed that misclassification of ulcer conditions is common [32]. A weakness in this trial is consequently that the review of medical records implied subjective estimation on a few patients that were not directly diagnosed
according to the ICD system, which is why the medical description in text had to constitute the background to inclusion or exclusion in these situations.

When a patient with hematemesis and melena at the Emergency Department is further examined through EGD at the surgical ward, the ICD codes for these conditions (K92) are registered at the Surgery Department if the bleeding is not very prominent, as a sign that a bleeding session however has occurred. The ICD codes for hematemesis and melena might therefore not be registered in terms of all bleeding conditions at the Surgery Department, since the ICD codes K25, K26 and K28 are used instead. For this reason, investigation including an expanded study population is required to cover even this group of bleeding patients.

A considerable group of individuals is necessary to achieve statistic power and clarify the significance of TXA in the context of bleeding ulcer disease. Further studies are required to explain the role of TXA in bleeding ulcer conditions, since the medication has been proven to be fortunate for bleeding episodes in other parts of the body, as well as it has been suggested to have a positive effect even in the acidic GI system. Nevertheless, this retrospective study was a prerequisite part of a broadened study, since patients that would not have been discovered by using other ICD codes for bleeding conditions in the upper GI tract, were identified in this study. The risk of thromboembolism after treatment with TXA, which has been examined and negated in some studies [24], was not investigated in the present study and requires to be further evaluated if new TXA recommendations will be appointed.

CONCLUSION

In conclusion, the prescription of Cyklokapron has declined after the publication of the Meta analysis from The Swedish Council on Health Technology Assessment. Variations in the prescription habits, however, indicate that there is a prevailing insecurity among the clinicians concerning TXA and when it is supposed to be prescribed to generate the best, possible result for patients with bleeding ulcer disease. This retrospective study could not conclude the significance of TXA on patients with bleeding ulcer disease. Present results indicating that some of the outcome factors were not improved in the group treated with TXA, in comparison with the control group, were probably a consequence of a higher co-morbidity in the group treated with TXA. There is still possible that TXA might have had a beneficial effect on these patients. Further investigation, including an expanded group of ulcer patients, is necessary to be able to confirm the role of TXA in bleeding ulcer conditions.
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