Efficacy and safety assessment of α-chymotrypsin injection in postoperative and post-traumatic edema: a prospective, open-label, multicenter observational registry study in Egypt

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Background
Edema occurs because of trauma to tissues from an injury or a surgical procedure and is bothersome to both patients and treating physicians. The presence of edema is an initial component of the inflammatory response to tissue trauma. Chymotrypsin possesses potent anti-inflammatory properties that accelerate the reabsorption of inflammatory edemas as well as postoperative and post-traumatic hematomas and edemas. This study is a pioneer research to evaluate the efficacy and safety of α-chemotrypsin injection in postoperative and post-traumatic edema.
Patients and methods
A total of 529 patients with postoperative and postfracture edemas were recruited from three centers in Egypt (Orthopedic, Gynecology, and Surgery). Edema grades during visit 1 (V1) and visit 2 (V2) were evaluated and given scores from 1 to 4; their mean values were obtained and compared using the paired *t*-test for the overall sample, for each center, and by nature of edema (postoperative and post-traumatic).
Results
Of the 529 patients, 523 (98.9%) cases improved, six (1.1%) cases did not change, and the condition of no patient worsened. The mean edema grade score in V1 in the overall sample was 2.75, which decreased to 1.53 in V2 ($P<0.001$), with a percent change of –61%. There was a statistically significant difference in edema grade between V1 and V2. No adverse events or serious adverse events were reported during the study.
Conclusion
α-Chymotrypsin ampoules from Amoun are effective in lowering the edema grade and in managing patients with postoperative edema and postfracture edema as well.

Keywords:
α-Chymotrypsin, chymotrypsin, edema, fractures, inflammation, surgery, trauma

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Background

Edema occurs because of trauma to tissues from an injury or a surgical procedure, which is bothersome to both patients and treating physicians. Trauma to tissues causes increased capillary permeability or capillary rupture, which burdens a healthy lymphatic system as fluids and protein leak into tissue spaces. Temporary block or damage to the neighboring lymphatic tissue reduces protein and fluid uptake, causing a disruption in Starling's equilibrium as well as swelling [1,2]. Presence of edema is the primary element in the tissue trauma inflammatory response [3–5]. Edematous fluid causes further complications in soft tissue and joint structures if persistent beyond the typical healing period. The manifestation of lengthy edema after surgery or trauma is clinically significant as it can compromise recovery as it delays wound healing and stimulates pain receptors by pressuring neuroreceptors causing pain [5–9]. Finding the most suitable treatment to prevent persistent edema is challenging. There are many traditional treatment methods for edema resolution, such as physiotherapy, chemical modalities suchas NSAIDs, and enzyme preparations [10,11]. Chymotrypsin has potent anti-inflammatory properties that accelerate the reabsorption of inflammatory edemas as well as of postoperative and post-traumatic hematomas and edemas. Moreover, chymotrypsin has proteolytic activity that enables the destruction of the fibrinous formations resulting from subacute or chronic inflammatory processes [12].This study is to confirm the efficacy and safety of α-chymotrypsin in patients with

post-traumatic edema, arthritis, and postoperative edema. In this study we wanted to primarily assess edema grade score improvement and rate of change after treatment with α-chymotrypsin Ampoules in patients aged 18–65 years.

Patients and methods

This is an open-label, noninterventional, multicenter survey conducted on patients having edema due to either operation or trauma. Approval from the ethics committee of the three centers and from the Ethics Committee of the Ministry of Health was obtained before the study. A total of 529 patients from three centers in Egypt were enrolled in this study from 28 August 2014 to 30 November 2015 (Table 1).

At initial visit (visit 1), patients underwent a history and physical examination, including complete examination of the edema; they had to mention whether it was postoperative or post-traumatic. Grade of edema was calculated (Tables 1 and 2 and Fig. 1).

An informed consent form was signed and the patient underwent investigations. The treatment regimen consisted of α-chymotrypsin 5 mg ampoules manufactured by Amoun Pharmaceuticals (Amoun Pharmaceutical Company, Obour city, Industrial zone (1), Cairo, Egypt) once a day for 1 week or as per the investigator's advice. α-chymotrypsin injection is packed as a box of three ampoules of 5 mg crystallized and lyophilized chymotrypsin (450 EA units)+three ampoules of 3 ml apyrogenic saline.

All patients were seen in the outpatient clinic by the investigators who assessed edema grade after 1 week from initial visit (visit 2). The patients were asked to return 30 days after initial study enrollment if needed for post-trauma or adverse events (visit 3). Most of the patients did not need be followed up with visit 3.

Table 1 Centers and number of patients

Centers	Site	Description	Number of enrolled patients
Surgery Center (Center 1)	Ain Shams University Hospital	Operations were performed in the abdomen and pelvis, neck, breast and upper and lower limbs	244
Obstetric Center (Center 2)	Al-Galaa Hospital	Operations were cesarean section, hysterectomy, laparotomy, and ovarian cystectomy	85
Orthopedic Center (Center 3)	Om Al-Masryin Hospital	Operations: open reduction and internal fixation procedures. These operations were performed in the upper limb and in the pelvis (101 patients)Traumas: open and closed fractures (99 patients)	200

Table 2 Edema grade score

Grades of edema	Description	Score
0	No edema	0
1+	2 mm or less: slight pitting, no visible distortion, disappears rapidly	1
2+	2–4 mm indent: somewhat deeper pit, no readably detectable distortion, disappears in 10–25 s	2
3+	4–6 mm: pit is noticeably deep. May last more than a minute. Dependent extremity looks swollen and fuller	3
4+	6–8 mm: pit is very deep. Lasts for 2–5 min. Dependent extremity is grossly distorted	4

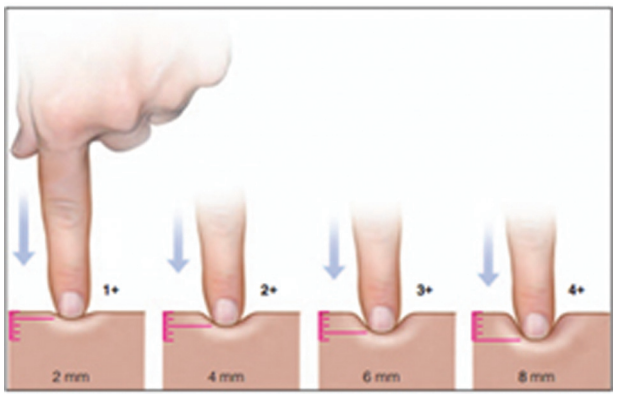
Statistical analysis

Data of 529 patients were analyzed in this study, which gives a margin error of ±4.8% at 95% confidence level and with expected number of patients with improving edema of 50%. Categorical data were presented as number and percentage and the χ^2-test (or its subsidiaries) was used to obtain *P*-values to test the significance of differences between centers and sample subsets. Descriptive statistics (mean±SD) presented the numerical data and the Student *t*-test (or its subsidiaries) was used to obtain *P*-values to test the significance of differences between centers and sample subsets. The calculation of statistics and proportions did not include the missing data.

Demography

The mean age of the participants was 42.38±12 years; 61.5% of patients in center 1, 41% of patients in site 3, and all patients of center 2 were female (Table 3).

Figure 1



Grading method: dent depth and duration.

Results

Of the 529 patients, 523 (98.9%) cases improved, six (1.1%) cases did not change, and none worsened. The mean edema grade score in visit 1 (V1) in the overall sample was 2.75, which decreased to 1.53 in visit 2 (V2), with a percentage change of −61%. The difference was very highly significant ($P<0.001$).

In the surgical center the mean edema grade score in V1 was 2.16, which decreased to 1.04 in V2, with a percentage change of 52%. In the Gynecology Center the mean edema grade score in V1 was 1.55, which decreased to 0.14 in V2, with a percentage change of −91. In the Orthopedic Center the mean edema grade score in V1 was 3.34, which decreased to 1.29 in V2, with a percentage change of −61%. The difference was very highly significant ($P<0.001$) in all centers.

As for edema indication, postoperative mean edema grade score in V1 was 2.29, which decreased to 0.92 in V2, with a percentage change of 60%. In post-traumatic edema, the mean edema score was 3.44 in V1, which decreased to 1.29 in V2, with a percentage change of −63%. The difference was very highly significant ($P<0.001$) for both indications.

No adverse events or serious adverse events were reported during the study time from V1 to V2 and for 30 days after the last dose of α-chymotrypsin had been received.

Discussion

The scope of this study was to evaluate the efficacy and safety of α-chymotrypsin in the management of postoperative and post-traumatic edema in patients aged 18–65 years. The patients were not suffering from any severe liver or kidney disease, nor were they allergic to chemotrypsin. The study enrolled 529 patients; no patients terminated their participation in the study, nor were any lost to follow-up. Among the 529 patients 523 (98.9%) cases improved, six (1.1%) cases did not change, and no cases worsened. Our study is a pioneer investigation into the efficacy of α-chemotrypsin injection, as we could not find any similar studies conducted to assess the efficacy of α-chymotrypsin intramuscularly. Edema grade score dropped from 2.75 in V1 to 1.53 in V2 in the overall sample and the difference is very highly significant ($P<0.001$). There was 61% improvement in edema grade score and a change in edema grade in the overall sample as well.

α-Chymotrypsin showed significant improvement in edema grade scores and percentage change in edema score in all centers. Edema grade score improved by 52, 91, and 61% in center 1 (General Surgery),center 2 (Gynecology), and center 3 (Orthopedic), respectively (Fig. 2).

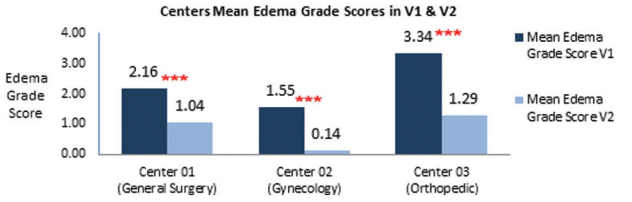
α-Chymotrypsin showed significant improvement in edema grade scores in both postoperative and postfracture groups, with the score improving by 60 and 63%, respectively (Fig. 3).

No adverse events or serious adverse events were reported for α-chymotrypsin in the study.

Table 3 Demography of patients in the three centers

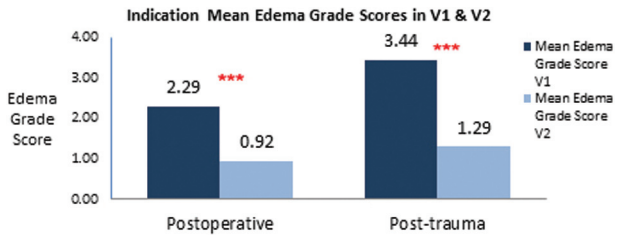
	Center 1	Center 2	Center 3
Sex [*n* (%)]			
Male	94 (38.5)	0 (0)	118 (59)
Female	150 (61.5)	85 (100)	82 (41)
Age (years) [*n* (%)]			
Mean±SD	45±10.564	36±11.1	29±7.696
<36	60 (24.6)	52 (61.2)	74 (37)
36–50	103 (42.2)	24 (28.2)	68 (34)
>50	81 (33.2)	9 (10.6)	58 (29)
BMI [*n* (%)]			
Mean±SD	29.1±5.4	28±46	20±46
Normal	64 (26.2)	12 (14.1)	23 (11.5)
Overweight	111 (45.5)	24 (28.2)	135 (67.5)
Obese	69 (28.3)	49 (57.6)	42 (21)

Figure 2



Percentage change in edema grade score by center. V1, visit 1; V2, visit 2.

Figure 3



Mean edema grade scores by indication in V1 and V2. V1, visit 1; V2, visit 2.

Limitation

This study was an observational rather than an interventional study, and therefore suffered from a number of limitations. We tried to consider most of the variables that may affect the endpoint; however, there were many variables that were not counted, such as differences in clinical practice between study investigators, lifestyle, diet-style factors, and socioeconomic status. Furthermore, the proportion of patients' sample subsets was not ascertained. Center 2 enrolled 85 patients (20% of total sample).

As there were no similar studies assessing the same objective, we were not able to compare our study results with previous study findings.

Conclusion

α-Chymotrypsin ampoules of Amoun are safe and effective in lowering edema grade and in managing patients with postoperative edema and postfracture edema as well.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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