MANAGEMENT OF CHRONIC ANAL FISSURE BY CHEMO-DENERVATION OF THE INTERNAL ANAL SPHINCTER USING BOTULINUM TOXIN A
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ABSTRACT

Anal fissure is one of the commonest causes of difficult and painful defecation in our community that starts as a crack in the anal canal mucosa and resist healing. Exact pathogenesis is unclear but recent theories for non-healing include sphincter hypertonicity and poor stretchability together with mucosal ischemia. Surgical sphincterotomy remains the gold standard as a definitive treatment but it has considerable risk of incontinence. The idea of chemo-denervation of internal anal sphincter by botulinum toxin to achieve chemical sphincterotomy is developing as a safe, easy and outpatient procedure with lower complication and comparable success rates as surgery that may be used as a treatment to avoid surgery. **Aim of the study:** to assess chemo-denervation of internal anal sphincter by local injection of botulinum toxin A as an effective treatment for anal fissure. **Patients and methods:** 60 patients underwent treatment by 20-40 IU (average 30 IU) of botulinum toxin A injected on both sides of the fissure. All patients were observed in the surgical ward for 3-6 hours and discharged in the same day with follow up at outpatient clinic after 1, 2, 4, 6 and 8 weeks and after three and six months for pain, bleeding, headache, discharge, incontinence, relapse, infection, spasm and degree of healing. If no improvement and/or healing was obtained, injection was repeated 3 months after the first injection and follow up is continued. Collected data are statistically analysed and presented in the form of mean and standard deviation. The significance test considered statistically significant if the P value is less than 0.05. **Results:** Patients in the study (60 patients) were 27 males (45%) and 33 females (55%) with mean age (34.7) years. After the 1st injection complete healing occurred in 39 patients with success rate 65% at 3 months’ follow-up with an average healing time of 6.4 weeks. Second injection was needed in 21 patients and done 3 months after 1st injection. Healing occurred in 9 patients with healing rate of 42% 3 months after the second injection at the end of the study. The total healing rate of the study 80% (48 patients). The recurrence rates were 16.6% (8 patients) at 6 months after the 1st and 2nd injections. No improvement was observed (no symptomatic relief nor healing) in 12 patients after 2 injections with failure rate of 20%. A total of 2 patients developed transient flatus incontinence after the 1st injection and spontaneously resolved within 6 days. 2 patients showed severe pain after injection which responded to analgesics. However, all patients there were marked improvement of pain by the 2nd week with no major complications. **Conclusion:** It is that botulinum toxin injection is a safe, easy and effective treatment for chronic anal fissure and it should be considered the first-line therapy in patients with chronic anal fissure. Further long term studies on large number of patients are needed to assess relapse rate and causes and to compare the results with that of surgery as a definitive treatment.

**Key words:** anal fissure, chemo-denervation, botulinum toxin, sphincterotomy.

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**INTRODUCTION**

Anal Fissure is a longitudinal tear or ulcer extending below at the margin of the anus. It is more common in women than men. It is the commonest cause of a severe anal pain, but its exact incidence is unknown (5). Anal fissures make more than 15% of rectocolic consultations and it affects all age groups (2).

Fissure may be classified into 2 types, acute and chronic. In 6 – 8 weeks, an acute anal fissure, which is superficial wound in the skin, can become chronic. A chronic AF has indurated edges caused by the exposure of anal sphincter fibers (3).

Anal fissures cause pain at defecation and rectal bleeding. Fissure commonly arise in the posterior position of the anus and it is thought to occur secondary to ischemia as a result of increased anal sphincter pressures and decreased blood flow (4).

The primary causes include trauma of the anal canal by constipation (25% patients with chronic AF have constipation), the water stream in a bidet-toilet, childbirth, Diarrhea after bariatric procedures (6%) (5).

Medications used for treatment reduce anal resting anal sphincter pressure but the result is not satisfactory in most cases. So, the gold standard in treatment was surgical sphincterotomy. In the last 2 decades, new concept of treatment of chronic anal fissure by chemodenervation of the internal anal sphincter using Botulinum Toxin was assumed as a
relevant option for treatment with promising results (6).

BACKGROUND
It has been proved that hypertonicity of the internal anal sphincter (IAS) is involved in the pathogenesis of fissure. This has been substantiated by successful surgical treatment with internal sphincterotomy which generally results in a reduction of resting anal pressure (5). Mucosal ischaemia has also been supposed to result in the non-healing of anal fissure and progress of an acute anal fissure to a chronic type (8). Assessment of microvascular perfusion of the anal canal by laser Doppler flowmetry demonstrated significantly low anal blood flow at the fissure site and showed that IAS resting pressure is inversely related to the blood flow (9).

A lot of medication applied for topical therapy of anal fissure causes IAS relaxation. Because it mimics surgical sphincterotomy, this process is called pharmacological (or chemical) sphincterotomy. It may be performed with botulinum toxin (BTX) injections or the topical application of ointments such as calcium blockers, nitric oxide donors, a potassium channel agonist (minoxidil), inhibitors of angiotensin-converting enzyme, phosphodiesterase inhibitors, cholinomimetic (bethanechol) and an adra-nergic antagonist (indoramin) (10).

Upon these facts, medications were used topically or orally reduce anal resting pressures in patients with anal fissure. For example, Indoramine, reduces anal resting pressure by 35.8% in patients with anal fissure. However, in many clinical trials, satisfactory results were not observed despite significant reductions in anal resting pressure (11).

Research continued to discover the cause of this results and verify the exact pathogenesis of fissures. A study performed by Thornton et al. showed no direct relation between healing, incontinence and significant reduction in anal resting pressure (only 17%) (12). Another study showed that healing is not dependent on the level of resting anal pressure and no statistically significant differences between healing and non-healing of chronic AF after lateral internal sphincterotomy based on manometric and endosonographic findings (8).

This led to development of a new approach of healing based on chemical point of view from the angle of biochemistry to understand the anal fissure origin. There was a theory of endothelial cell dysfunction with reduced synthesis of nitric oxide. Another theory says that sphincter is hypersensitive to beta 2 agonists so, in psychological stress there is sustained tonic rise in anal pressure and may cause molecular changes in beta 1 adrenergic receptors. (9).

Recent theory of poor sphincters stretchability and chemical mediators of inflammation and relationships between these elements as the main cause of non-healing was postulated by Minguez et al. when they reported that 30% of fissure cases occur with a low or normal anal sphincter pressure (13).

Poor stretchiness of the anal sphincters leads to damage of tissues in the fissure region during defection and causes release of mediators such as adenosine diphosphate (ADP), adenosine triphosphate (ATP), 5-hydroxytryptamine (5-HT), platelet activation factor, as well as thrombin and substance P, cause contraction of smooth muscles of sphincters and vessels resulting in non-healing due to ischemia and pain and difficult defecation due to spasm. Diminished production of NO and microvascular damage activates thrombin production which stimulates endothelial cell contraction. (14).

Hypothesis suggesting that Clostridium botulinum toxin is considered as a successful pharmacologic sphincterotomy since thrombin-stimulated endothelial cell contraction could be abolished by Clostridium botulinum toxin and also the toxin reverses hypoxia induced by a decrease in NO expression (15).

Botulinum toxin is the most toxic protein known produced by Clostridium bacteria which is responsible for the pathophysiology of botulism. It enters peripheral cholinergic nerve terminals, to produce reversible inhibition of neurotransmitter release. It is useful therapeutic agents for diseases caused by hyperactivity of cholinergic nerve terminals (16).

Although Botulinum toxin type A is one of the most potent biologic toxins, it has become a safe and effective therapeutic drug in the treatment of many different indications and it has also been used as life-enhancing cosmetic drug. It has been found to be of therapeutic value in the treatment of a variety of neurologic and ophthalmologic disorders. The Food and Drug Administration recently approved botulinum toxin as a therapeutic agent in many spastic disorders (17).

The therapeutic potential of botulinum toxin (BT) for skeletal muscle disorders was first realized in the 1970s, later, it was also shown to be effective in the gastrointestinal tract (GIT). It was considered by some authors as an
innovation equal to introduction of laparoscopic surgery because it made the treatment of several clinical conditions easier, in the outpatient setting, at a lower cost and without permanent complications (18).

Botulinum toxin blocks excitatory neurotransmitter release to restore the balance and cause a decrease in the resting tone of the muscle involved. Although Botulinum toxin can clearly inhibit the release of acetylcholine, little else is known about its effects on nitric oxide (NO) release. Also its effects on other neurotransmitters has not been well documented (19).

The exact mechanism of botulinum toxin on anal sphincters is not completely understood (20). It may inhibit release of neurotransmitters from adrenergic nerves directly causing inhibition of its activity in muscle contraction (21). It is supposed that the it diminishes concentration of noradrenaline and inhibits prolonged internal sphincter contraction and release of mediators (22).

AIM OF THE STUDY

to assess chemodeneration by botulinum toxin as an effective treatment for anal fissure with high success low complication rates.

PATIENTS AND METHODS

A prospective study was carried out in General Surgery Department, Al-Hussien University Hospital, Cairo, Egypt. A total of 60 patients diagnosed clinically as chronic anal fissure not responding to conservative treatment had been included in the study. Patients underwent treatment by local injection of botulinum toxin type A.

Inclusion Criteria:

• Patients with chronic anal fissure.
• Patients having symptoms not improved by conservative treatment.
• Patients unfit for surgery.
• Patients refusing surgical interference.
• Recurrence after surgery.

Exclusion Criteria:

• Patients under age of eighteen years.
• Patients with history of anorectal operations.
• Patients with associated anorectal problems (piles, fistulas….etc.).

Procedure:

The anal area was locally anesthetized by injection of 5-10 ml of 1% lidocaine with epinephrine. The anal sphincters were located by palpation. A total dose of 20-40 IU (average 30 IU) of botulinum toxin A was diluted in 20 ml normal saline and injected at 2 sites around the anus on both sides of the fissure by using insulin syringe while the patient was laying on his/her left side and circumferentially. All patients were observed in the surgical ward for 3-6 hours. Occurrence of urine retention, hypotension, headache or other complications was recorded. Analgesics were given according to patient need. Discharge in the sameday with follow up at outpatient clinic after 1, 2, 4, 6 and 8 weeks and after three and six months. If no improvement and/or healing was obtained, injection was repeated 3 months after the first injection and follow up is continued.

Data were collected as regard pain, bleeding, headache, discharge, incontinence and relapse. Pain assessment was performed using a visual analog scale (VAS) with which each patient noted the severity of pain, using a linear scale between zero and 10. This scale asks the patient to assign a number from zero to ten according to the severity of pain. ‘Zero’ means you have no pain at all while ‘Ten’ means the worst possible pain you can image. The values on the pain scale correspond to pain levels as 1 – 3 = mild pain, 4 – 6 = moderate pain, 7 – 10 = severe pain. Digital rectal examination (DRE) was done to detect infection, spasm and degree of healing. Healing was assessed on symptomatic relief and complete epithelialization on perianal examination. Recurrence was considered by recurrence of pain and/or reappearance of fissure after healing. Informed consent had been obtained from all patients and they had been informed all details about the study and the trial protocol had been approved by the institutional ethics committee. DF significant for the qualitative data, the quantitative data were presented in the form of mean and standard deviation. The significance level will be determined at 95% so, the significance test considered statistically significant if the P value is less than 0.05.
**RESULTS**

Total number of patients in the study was 60 patients; 27 males and 33 females with mean age 34.7 years.

**Table (1) demonstrates the gender distribution of the study.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency</th>
<th>Valid Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>33</td>
<td>55.0</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>45.0</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table (1): Gender Discription.**

From the table we can see that 55% of the patients were females while 45% of the patients were males. After the 1st injection complete healing occurred in 39 patients at 3 months’ follow-up with an average healing time of 6.4 weeks. Second injection was needed in 21 patients and done 3 months after 1st injection. Healing occurred in 9 patients 3 months after the second injection at the end of the study. So, healing occurred in 48 patients. Failure (no symptomatic relief nor healing) was observed in 12 patients after 2 injections.

**Table (2) shows the description of the healing and failure rates from both injection settings.**

<table>
<thead>
<tr>
<th>Healing from injection</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healing from 1st injection</td>
<td>39</td>
<td>65.0</td>
<td>65.0</td>
<td>65.0</td>
</tr>
<tr>
<td>Healing from 2nd injection</td>
<td>9</td>
<td>15.0</td>
<td>15.0</td>
<td>85.0</td>
</tr>
<tr>
<td>Failure</td>
<td>12</td>
<td>20.0</td>
<td>20.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table (2): Healing and failure Rates**

From the table we can see that 65% of the patients were healed from the first injection while 15% were healed from the second injection while 20% have not been healed. The results are shown in the graph (1).

**Graph (1): Healing and Failure Rates.**

The recurrence after complete healing occurred in 8 patients of the 48 patients showed complete healing after the 1st and 2nd injection settings at 6 months. Table (3) describes the rates of the healing, recurrence and failure.

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healing with no recurrence</td>
<td>40</td>
<td>66.7</td>
<td>66.7</td>
</tr>
<tr>
<td>Healing followed by recurrence</td>
<td>8</td>
<td>13.3</td>
<td>13.3</td>
</tr>
<tr>
<td>No healing ( failure)</td>
<td>12</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table (3): Healing, recurrence and failure.
From the table we can see that 66.7% of the patients had no recurrence while 13.3% have recurrence after healing while 20% showed failure of the treatment.
A total of 2 patients developed transient flatus incontinence after injection and spontaneously resolved within 6 days. 2 patients showed severe pain after injection which responded to analgesics. However, all patients there were marked improvement of pain by the 2nd week mean pain score become 1.6 compared to pre-management score 6.5. There were no major complications following injection including hematoma-infection, flatus, fecal, and urinary incontinence after 2 weeks and 3 months.

**Table (4) demonstrates the description of different complication rates**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non</td>
<td>56</td>
<td>93.3</td>
<td>93.3</td>
</tr>
<tr>
<td>Transient flatus incontinence</td>
<td>2</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Severe pain</td>
<td>2</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table (4): The complication rates**
From the table we can see that 93.3% of the patients had no complication after the injections while 3.3% have transient flatus incontinence after injection which resolved within 6 days, while 3.3% of the patients showed severe pain after injection which responded to analgesics and improved by the 2nd week.

Chi-Square Tests had been done for Gender and Recurrence results. The value of Asymptotic Significance (2-sided) = 0.058 is higher than (α=0.05) so we will accept the null hypothesis so there is no relation between the gender and the Recurrence.

Chi-Square Tests had been done also to show relation between Gender and Complications. The value of Asymptotic Significance (2-sided) = 0.427 is higher than (α=0.05) so we will accept the null hypothesis so there is no relation between the gender and the Recurrence.

**DISCUSSION**
Chronic anal fissures are painful and can cause marked pain and distress for patients. Anal fissure is associated with higher anal sphincter tone and decreased internal sphincter relaxation \(^{(23)}\).
In some authors’ opinion \(^{(24)}\) high anal rest pressure is a result of the fissure and not a cause. A reduction in local blood flow measured by Doppler measurements is claimed to be another cause of the non-healing \(^{(25)}\). Anyhow, anal fissure is associated with internal sphincter hypertonicity and that is why surgical internal sphincterotomy has become the treatment of choice for anal fissure with healing rates of 91–95% despite this it is associated with higher rates of incontinence \(^{(26)}\).

Incontinence is the main side effect of surgery and in a meta-analysis the overall continence disturbance was 14%. This included flatus and fecal incontinence \(^{(27)}\). Incontinence may be immediate or a late complication following fissure surgery \(^{(28)}\).
Due to the rate of incontinence and the invasiveness of surgery, non-surgical measures have been used such as nitric oxide donors such as glyceryl trinitrate/nitroglycerin (GTN) and calcium channel antagonists that could be able to heal the fissure \(^{(29)}\). Also, the concept of pharmacological sphincterotomy by injection of botulin toxin is rising. The toxin injection causes relaxation of the sphincters and improves local microcirculation enhancing healing process \(^{(30)}\). Benefits of local toxin use include minimal to low risk of permanent incontinence, minimally invasive and treatment is easy to re-administer if failed initially. Recently the American Gastroenterological Society and The Association of Coloproctology of Great Britain and Ireland, recommended to try the use of a GTN treatment and Botulinum Toxin administration to patients with chronic anal fissure before undergoing surgery \(^{(31,32,33)}\).

In view of all this, we decided to perform this study using the local injection of Botulinum Toxin to outpatients in our hospital. The aim of this study was to report and to assess the effect of Botox as a single treatment for chronic anal fissure as regard success rate, duration of healing, possible complications and incidence of recurrence after short term follow up.

In previous study by Piccinni et al., they used botulinum toxin for 60 patients, after 1st injection 21 patients presented a complete healing of the fissure (35%) in the period ranging between the 3rd and the 4th week from treatment; 5 patients (8.33%) showed complete regression of symptoms and complete wound healing that occurred after 40-50 days. Three patients had thrombosis and healing occurred after a period of 50-60 days. Thirty-one patients
(51.6%) needed 2nd dose, 20 patients showed complete healing at 4-5 weeks from the second injection and 11 patients needed surgery because of a persistent pain. The total healing rate of 48.33% after the first inoculation with a 33.3% increase of healing after the second treatment with a failure rate of 18.33% (34).

The results of our experience were favorable as evidenced by the data. We obtained the healing of 48 patients out of 60 treated with one or two injections. After the 1st injection complete healing occurred in 39 patients with success rate 65% at 3 months follow-up with an average healing time of 6.4 weeks. Second injection was needed in 21 patients and done 3 months after 1st injection. Healing occurred in 9 patients with healing rate of 42% 3 months after the second injection at the end of the study. The total healing rate of the study 80% (57 patients). In our experience, we could not recognize factors or conditions that determine the non-healing of the fissure in 12 persons out of 60.

Another topic of the study was to discuss average healing time obtained by botulinum toxin injection. We noticed that patients responded well to the toxin and healing was observed in the first 2 months in 16 patients (35%), on the contrary another group of 15 patients showed the closure of the tear after a second injection thus after 3-4 months (31.2%). Analyzing the charts and the interviews with them, the only explanation of this difference seems to be linked to a lack of observation of hygiene rules (diet, baths etc.)

Likely, in the study of Glover et al., of 75 patients, the success rate was 90.7% at 3 months follow-up with an average healing time of 6.2 weeks (39). The healing rate was 81.3% at 3 months with the second injection at a longer duration. The major side effects of the toxin injection are gas incontinence but in all similar studies it was reversible when the toxin and the anal continence is completely returned to normal (35, 36).

In our study there was only temporary mild complications in the form of severe pain in 2 patients that improved at 9-12 days. Also, there was incontinence to flatus but not to stool in 2 patients and resolved spontaneously in few days. In a study performed in France at 2014 to compare the result of Botulinum toxin injection Lateral internal sphincterotomy is more effective with 1.3 greater chance of healing and a recurrence rate six time less frequent than with Botox treatment. However, the risk of anal incontinence for gas is nine times more common with sphincterotomy (38).

The recurrence rates were 20.6% and 12.5% at 6 months after the 1st and 2nd injections respectively.

In other study, a total of 6 patients developed transient flatus or fecal incontinence after the 1st injection, but shortly resolved within 7 days. There were no major complications following both procedures including hematoma, infection, flatus, fecal, and urinary incontinence after 2 weeks and 3 months (39).

Some authors report a certain incidence of relapse is up to the figure of 55% but in our study with short term follow up for 6 months we observed 8 relapses and planned them for surgery. We believe that the decline in rate of relapses may be due to an aggressive dietary control and to the particular attention paid to evacuation. Patients were worrying of suffering fissure again! Other longer studies show variable relapse rates so we recommended to have long term studies with stricter follow up to get more accurate and reliable results (40).

In a study compared botulinum toxin injection and surgical sphincterotomy, healing rates were similar in both groups at 6 months with 10 of 61 patients needed a second Botulinum toxin injection. However, the success rate was higher at 1 and 2 months in the surgery group compared with the BT Group. The response to botulinum toxin was not as durable as surgery falling to a success rate 75.4% after 1 year with 7 recurrent cases with botulinum toxin, while it was stable in the surgery group. Sphincterotomy was associated with a significantly higher complication rate (41).

Thus, it appears that sphincterotomy is more durable option but more complications were recorded. Some investigators have preferred surgery in young patients and with high resting sphincter pressure, as it is a risk factor could lead to recurrence. Botulinum toxin injection may be beneficial for older patients they have higher risk of incontinence.

A recent meta-analysis revealed that Surgery has a better healing rate and recurrence rate, while botulinum toxin treatment is better than sphincterotomy in complication rates and incontinence rates (42).

Thus, botulinum toxin offers to patient with anal fissure include a good tolerance, an outpatient procedure, and a lower complication rate (43).

In another recent study, botulinum toxin injection was used also as a diagnostic tool to detect patients who would not benefit from...
surgery if developed temporary incontinence on botulinum toxin injection. Combination of nitroglycerine and botulinum toxin injection has been evaluated; it results in increase in the rate of healing. Nelson et al. assumed that botulinum toxin injection is efficacious in the treatment of anal fissure. Response rates were greater than 60% at 2 months with better response to re-treatment so, the study considered botulinum toxin a viable treatment when other conservative treatment measures fail. However, the researchers considered botulinum toxin injection as a first-line treatment In elderly people, because the rates of fecal incontinence are high with sphincterotomy. Surgery is still the most durable treatment option, but the risks of fecal incontinence must be weighed against the benefits of the procedure. So, from this study and according to many authors, all patients should be treated medically first. Mishra et al. concluded in their study that combination treatments (NO donors and BT) should be used as first-line treatment despite being less effective than surgery. On other hand, the results of some trials are disappointing. Nelson and coworkers concluded that “medical therapy for chronic anal fissure may be applied with a chance of cure that is only marginally better than placebo." However, such conclusion was too pessimistic, and further multi-center trials with appropriate methodology and adequate follow-up are needed to ascertain efficacy of the treatment. Furthermore, the use of combined treatment modalities allowed up to 75% of patients to avoid sphincterotomy. As regard cost effectiveness, it appears that botulinum toxin use is cost-effective and it reduces the number of patients who need further surgery. The results of this study could help colo-rectal surgeons to change their beliefs about priority of surgery in treatment of chronic anal fissure. We suppose that before performing an operation, a pharmacological sphincterotomy, whether it be GTN, botulinum toxin injection or combination of both, must be attempted. With this technique we could definitively avoid surgery for most of anal fissure patients.

CONCLUSION

It is that botulinum toxin injection is a safe, easy and effective treatment for chronic anal fissure and it should be considered the first-line therapy in patients with chronic anal fissure. There are few randomized, controlled studies, and most reports in the literature contain small numbers, making conclusions about efficacy difficult so, further long-term studies on large numbers of patients are needed to assess relapse rate and causes and compare the results with that of surgery as a definitive treatment.

REFERENCES


