*G Chir Vol. 41 - n. 1 - pp. 118-125*
*January-February 2020*



# Relief of hemorrhoid symptoms: pilot study of a new topical ally

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SUMMARY: **Relief of hemorrhoid symptoms: pilot study of a new topical ally.**

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Aim. *The pathogenesis of hemorrhoids involves vascular congestion, fragmentation of supporting tissues and, in many cases, increased resting anal pressure. A new ointment (Hemolen®) has been devised to control hemorrhoids symptoms acting on all the pathophysiologic mechanisms involved.*

Methods. *Pilot study on patients with grade I-III hemorrhoids. The ointment was applied twice daily for 30 days and follow-up visits were scheduled 7 days (T1), 14 days (T2) and 30 days (T3) after recruitment (T0). Signs and symptoms (bleeding, discomfort, itching, edema, thrombosis, congestion, inflammation, pain) were evaluated at each visit using dedicated scores and VAS scale. Resting anal pressure was measured at time T0, 1 hour after the first application and at T1. Use of painkiller was recorded.*

Results. *48 patients (25 females; mean age 47±15.8 years) were enrolled; 52.1% of them had II degree hemorrhoids and 27.1% had III degree hemorrhoids. The severity scores significantly dropped from T0 to each scheduled visit and a significant reduction of resting anal pressure was observed from T0 to 1 hour after application ($z=13.5$; $p<0.001$) and from T0 to T1 ($z=6$; $p<0.001$). The comparison of the resting pressure among whole time series showed a significant reduction ($Fr=124.4$; $p=<0.001$). Use of pain-killers decreased significantly from T0 to T1 ($p<0.001$) and from T1 to T2 ($p=0.001$).*

Conclusion. *The new ointment tested in the present study is safe and effective for the management of hemorrhoid symptoms in the early stages hemorrhoids, during the acute phases and in patients with more severe hemorrhoids awaiting surgery. Prospective, randomized controlled trials are needed to confirm these encouraging results.*

KEY WORDS: Hemorrhoids - Hemorrhoidal disease - Hemorrhoidal crisis - Anal pressure - Anal tone - Topical drugs - Ointment - Conservative treatment.

## Introduction

Hemorrhoids are one of the most common and widespread benign anorectal diseases. Their typical signs and symptoms - bleeding, pain, itching, discomfort and prolapse - can have a major effect on patients' quality of life.

While the epidemiological data are difficult to assess definitively, the incidence of the disease is rising, especially in Western countries, in the highest socio-economic populations, in pregnant women and in constipated patients. A prevalence of 4-36% is reported in the international literature (1).

The etiology is still debatable: many theories have been investigated in recent decades in order to find an appropriate treatment to control the symptoms.

The most popular theories are the "sliding anal lining theory" and the vascular theory which explains prolapse and bleeding. However, more recently the role of the supporting tissues of the hemorrhoids (collagen fibers and extracellular matrix) has been emphasized: in fact, the inversion of the ratio between type I and type III collagen and the deterioration of the extracellular matrix, seem to have a crucial role in the prolapse of the hemorrhoidal cushions (1, 2).

Increased resting anal pressure also plays a part. Some Authors, in fact, have demonstrated that patients with congested or thrombosed hemorrhoids have higher resting anal pressure than healthy controls. In these patients, the internal anal sphincter

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hypertonia seems to hinder the repositioning of the hemorrhoidal cushions within the anal canal at the end of defecation, leading to vascular congestion, hemorrhoidal swelling, pain, discomfort and bleeding (3-7).

During the acute phase, known as "hemorrhoidal crisis", the impact on patients' quality of life can be so strong to impair activities of daily living (8).

The treatment of hemorrhoids depends on their severity, graded by Goligher's classification (9). Current international guidelines suggest that first and second degree hemorrhoids can be effectively managed by conservative treatment: adequate fiber and fluid intake, dietary and lifestyle changes and oral phlebotonics, are recommended to control these early stages. Non-responders to this treatment are candidates for more aggressive procedures such as rubber band ligation, infrared coagulation and sclerotherapy. Surgical options are reserved for third and fourth degree hemorrhoids, which can be considered "surgical stages" (10-12).

However, in the early stages and in the "hemorrhoidal crisis" the main goal of medical treatment is to control symptoms and avoid or postpone surgery; in patients who are awaiting surgery, conservative treatment could be a useful "bridge therapy" with the aim to control symptoms in the meantime they are waiting to be operated.

We believe that an effective therapeutic strategy to manage hemorrhoids and control the related symptoms, can only be developed if the main pathophysiological mechanisms are kept in mind: the aim of this pilot trial was to assess the safety and the effectiveness of a new topical treatment which has been designed to act on these mechanisms.

## Patients and methods

This observational, pilot study included 48 patients recruited according to the following criteria: both sexes, age between 18 and 85 years, grade I-III hemorrhoids and/or "hemorrhoidal crisis". The exclusion criteria were: grade IV hemorrhoids, pregnancy, anal abscess or fistula, anal fissure, anal incontinence, inflammatory bowel disease, colon, rectal or anal cancer, anticoagulant treatment or coagulation disorders, metabolic or endocrine disorders, liver disease and cirrhosis, HIV, previous anorectal surgery and/or radiotherapy of the pelvic and perineal region.

After obtaining their detailed written informed consent, the patients were evaluated at the baseline (T0) as follows: collection of medical history including current signs and symptoms, physical examination, anoscopy and anorectal manometry (ARM) performed using *Isolab HR* multichannel high resolution manometry *(Standard Instruments GmbH, Karlsruhe, Germany)*. Measurements were made using water-perfused probes with sensors connected with a dedicated computer for pressure recording.

All the patients were than provided with tubes of the new ointment and were asked to apply 1 cm of ointment (about 1 gr) twice daily (every 12 hours) for at least 30 days using the measuring line printed on the tube.

The active substances in the ointment are: complex of oligopeptides with a *"botx-like"* action which block internal anal sphincter contraction and hence reduce resting anal pressure; an oligopeptide derived from Fibronectin to restore the supporting tissue; synthetic avenanthramide and antagonist of vanilloid receptors with an anti-inflammatory and antiitch action; horse Chestnut which has well-known phlebotonic and antioxidant effects.

Patients were also instructed on how to apply the ointment (into the distal anal canal and over the anal verge using a gloved finger) and received dietary and lifestyle recommendations, bulk laxative and Diosmine 1000 mg for use twice daily.

The efficacy of the treatment was assessed by comparing symptoms and clinical data before (T0) and after treatment at visit T1 (scheduled for day 7°), T2 (day 14°), T3 (day 30°); ARM was performed at the baseline (T0), 1 hour after the first ointment application (at the time of recruitment) and atT1 in order to measure the resting anal pressure.

Signs and symptoms (bleeding, itching, discomfort, presence of edema, thrombosis, congestion and/or inflammation of hemorrhoid piles) were logged on a dedicated scale of 0 to 3: 0 none; 1 mild; 2 severe; 3 very severe. Pain was scored from 0 to 10 using a 10-cm continuous linear visual analogue scale (VAS).

Use of painkillers and any side effects manifesting during the study period, were also recorded.

## Statistical analysis

Data were prospectively recorded on an Excel® spreadsheet and were analyzed by Stata SE14® statistical software. Continuous variables were expressed as mean±standard deviation (SD), range or median, interquartile range (IQR) and range; categorical data were expressed as proportion.

Skewness and kurtosis test were used to evaluate the distribution of continuous variables and, for those not normally distributed, a normalization model was set using logarithmic function. Student's T-test for paired samples (for variables with normal distribution or normalized) and Wilcoxon's signed rank test (for variables with non-Gaussian distribution) were used to compare continuous variables between each scheduled visit; the Friedman's test was used to compare continuous variables among whole time series and the Fisher's exact test was used to compare categorical data between each scheduled visit.

For all tests, a p- value <0.05 was considered significant.

## Results

In the period between January and July 2018, 48 consecutive patients (23 males, 25 females) with a mean age of 47.0±15.8 years (range: 22-81) met the inclusion criteria and were enrolled in the study. Most (52.1%) had II degree hemorrhoids, while 37.5% had "hemorrhoidal crisis". The patient's characteristics are summarized in Table 1.

All patients completed the follow-up at T3 and there were no adverse events and no drop-outs.

TABLE 1 - BASELINE PATIENTS' CHARACTERISTICS.

| | |
|---|---|
| **Number of patients enrolled** | 48 |
| **Gender; n (%)** | |
| • **females** | 25 (52.1%) |
| • **males** | 23 (47.9%) |
| **Age; mean±SD** | 47.0±15.8 |
| **Hemorrhoids' degree; n (%)** | |
| • **I degree** | 10 (20.8%) |
| • **II degree** | 25 (52.1%) |
| • **III degree** | 13 (27.1%) |
| **hemorrhoidal crisis; n (%)** | 18 (37.5%) |

The severity score for patients' signs and symptoms significantly dropped from the time of the recruitment (T0) to each scheduled visit (T1, T2 and T3), as summarized in Tables 2 and 3.

The median pain value (evaluated using the VAS scale) progressively decreased from 4 at T0, to 2 at T1 and 0 at T2 and T3 (Table 4) (Figure 1).

Use of pain-killers also decreased significantly from T0 to T1 ($\chi^2$=40.4; p<0.001) and from T1 to T2 ($\chi^2$=48.0; p=0.001) (Table 5).

A significant improvement in ARM data was observed after the application of the ointment with a drop in median resting anal pressure from 95 mm Hg at the baseline (T0) to 87.5 mm Hg after 1 hour of application and 80 mm Hg after 1 week (T1); the comparison of the pressure values among whole time series showed a significant progressive reduction (Fr=124.4; p<0.001) and the differences between T0 and 1 hour after application and between T0 and T1 were also statistically significant (z=13.5; p<0.001 and z=6.0; p<0.001, respectively) (Figure 2).

## Discussion

According to the main guidelines, the conservative treatment of first and second degree hemorrhoids is based on phlebotonic drugs that act on the vascular component, improving microcirculation, vascular tone and lymphatic drainage and protecting vessels from mediators of inflammation (1). The use of phlebotonics is also supported by systematic reviews and metanalyses (13, 14). In contrast there is a paucity of literature on topical treatments and the available studies are limited to small caseloads. Some studies of anesthetics, steroids, calcium dobesilate, herbal remedies, *Eschirichia Coli* suspension and hyaluronic acid (15-20) have been published with varying success rate reported.

Given the strong impact of symptoms on quality of life, topical ointments containing anesthetics, steroids and emollients for quick relief are commonly use in the acute phase. Ointments are often "self-prescribed" but some of them in the long term can lead to allergic reactions, discomfort and sensitization (1).

The use of sphincter relaxant ointments has also

Table 2 - SEVERITY OF SIGNS AND SYMPTOMS (MEAN SCORE ± SD AND RANGE) AT EACH SCHEDULED VISIT.

| | T0 | T1 | T2 | T3 |
|---|---|---|---|---|
| **Bleeding** | 2.1±1.1 (0 – 3) | 0.4±0.5 (0– 2) | 0.02±0.144 (0 – 1) | 0 |
| **Itching** | 2.7±0.8 (0 – 3) | 0.8±0.7 (0 – 2) | 0.06±0.24 (0 – 1) | 0 |
| **Discomfort** | 2.3±1.3 (0 – 3) | 0.4±0.5 (0 – 1) | 0.02±0.14 (0– 1) | 0 |
| **Edema** | 3.0±0.2 (2 – 3) | 1.5±0.5 (1 – 2) | 0.25±0.44 (0 – 1) | 0 |
| **Thrombosis** | 1.9±1.4 (0 – 3) | 0.5±0.6 (0– 2) | 0 | 0 |
| **Congestion/Inflammation** | 2.1±1.4 (0– 3) | 0.5±0.5 (0 – 2) | 0 | 0 |

**Key: 0: none; 1: mild: 2: severe; 3: very severe**

Table 3 - COMPARISON OF SIGNS AND SYMPTOMS AT EACH SCHEDULED VISIT.

| Time of evaluation compared | Bleeding | Itching | Discomfort | Edema | Thrombosis | Inflammation |
|---|---|---|---|---|---|---|
| **T0-T1** | z =6,1 p <0.001 | z = 6,1 p <0.001 | z = 5,8 p <0.001 | z = 6,2 p <0.001 | z = 5,4 p = <0.001 | z = 5,6 p <0.001 |
| **T0-T2** | z = 5,9 p <0.001 | z = 6,4 p <0.001 | z = 6,1 p <0.001 | z = 6,3 p <0.001 | z = 5,5 p =<0.001 | z = 5,8 p <0.001 |
| **T0-T3** | z = 5,9 p <0.001 | z = 6,5 p =0.001 | z = 6,1 p <0.001 | z = 6,8 p <0.001 | z = 5,5 p =<0.001 | z = 5,8 p <0.001 |
| **T1-T2** | z = 4,1 p <0.001 | z = 5,3 p <0.001 | z = 4,0 p <0.001 | z = 6,3 p <0.001 | z = 4,5 p =<0.001 | z = 4,8 p <0.001 |
| **T1-T3** | z = 4,2 p <0.001 | z = 5,4 p <0.001 | z = 4,1 p <0.001 | z = 6,2 p <0.001 | z = 4,5 p =<0.001 | z = 4,8 p <0.001 |
| **T2-T3** | z = 1,0 p = 0.317 | z = 1,7 p <0.001 | z = 1,0 p = 0.317 | z = 3.5 p = 0.001 | - | - |

been proposed in the acute phase and above all in the presence of thromboses (21). The main mechanism of action is a relaxation of the internal anal sphincter thus reducing pain.

Most research in this field has investigated nitric oxide donors such as Glyceryl trinitrate (GNT) (22), and calcium antagonists such as Nifedipine (21).

Although they are of proven efficacy, nitric oxide donors are associated with a high incidence of side effects such as headache and orthostatic hypotension (22, 23).

The use of topical GNT has also been suggested

TABLE 4 - COMPARISON OF PAIN BETWEEN SCHEDULED VISIT.

| Time of evaluation compared | Test | p |
|---|---|---|
| T0-T1 | t = 13.9 | <0.001 |
| T0-T2 | z = 6.1 | <0.001 |
| T0-T3 | z = 6.1 | <0.001 |
| T1-T2 | z = 5.7 | <0.001 |
| T1-T3 | z = 5.7 | <0.001 |
| T2-T3 | z = 2.4 | 0.014 |

for the control of post-operative pain after Milligan Morgan hemorrhoidectomy. Some studies found that surgical procedures increase the resting anal pressure and that anal spasm may be a main source of anal pain and delayed healing after hemorrhoidectomy (24-27). A more invasive procedure, based on botulinum toxin injection into the internal anal sphincter, has also been evaluated for the reduction of pain associated with high resting anal pressure in acute "hemorrhoidal crisis" with external thrombosis as well as after Milligan Morgan hemorrhoidectomy (28-30).

As previously stated, the pathophysiological mechanisms should be the main target of an effective treatment and the innovative ointment tested in this study could be a rational support in the management of hemorrhoidal symptoms because its main components act synergistically on the pathophysiological mechanisms underlying hemorrhoidal disease by combating the high anal resting pressure (responsible for pain and discomfort), reducing the vascular congestion (that causes bleeding), promoting the regeneration of damaged supporting tissue and modulating the itching pathways.

In fact, the oligopeptides complex consists of Acetyl Hexapeptide-8 (AH8) and Pentapeptide-18 (P18), with a similar action to botulinum toxin, reduces internal anal sphincter tone without the need for invasive procedures such as injection.

AH8 is a replica of the N-terminal segment of the SNAP 25 complex that forms the SNARE complex (membrane proteins), essential for the release of Acetylcholine (ACH) at the musculoskeletal synapse. AH8 competes with the natural proteins forming the "SNARE complex" thus blocking the

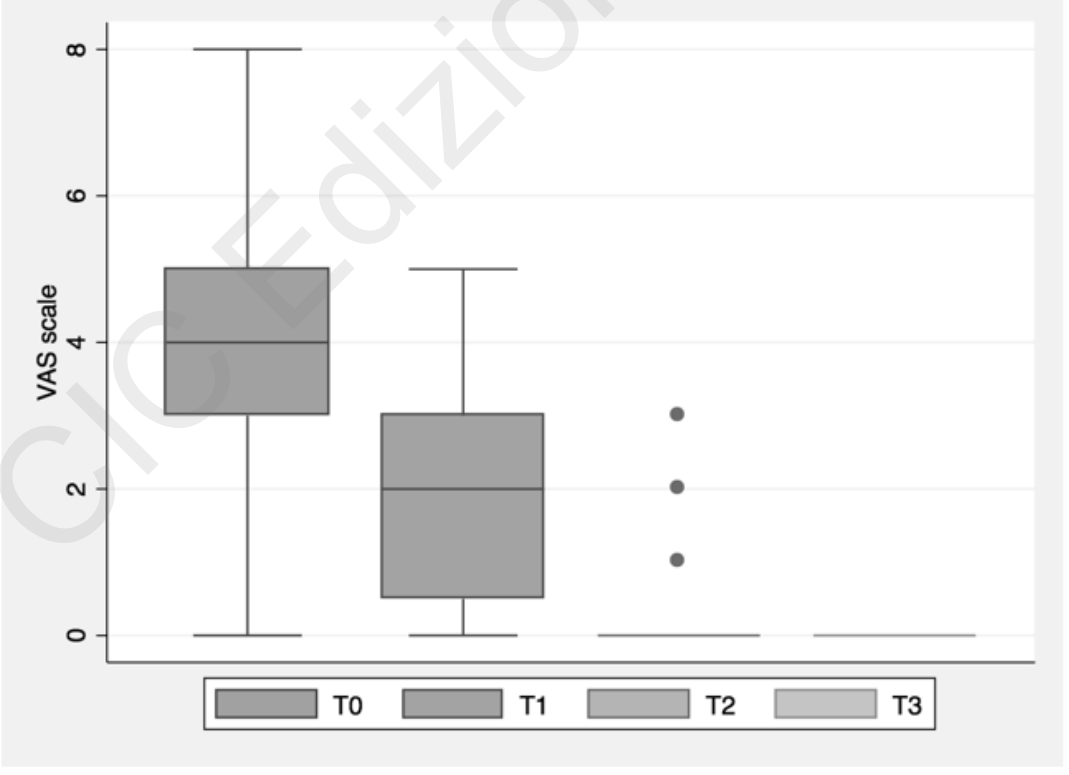


**Figure 1 - Median, range and IQR range of pain at each scheduled visit.**

TABLE 5 - REPORTED USE OF PAINKILLERS AT EACH SCHEDULED VISIT.

| Time of evaluation | Number of patients | % |
|---|---|---|
| **T0** | 21 | 43.8 |
| **T1** | 19 | 39.6 |
| **T2** | 2 | 4.2 |
| **T3** | 2 | 4.2 |

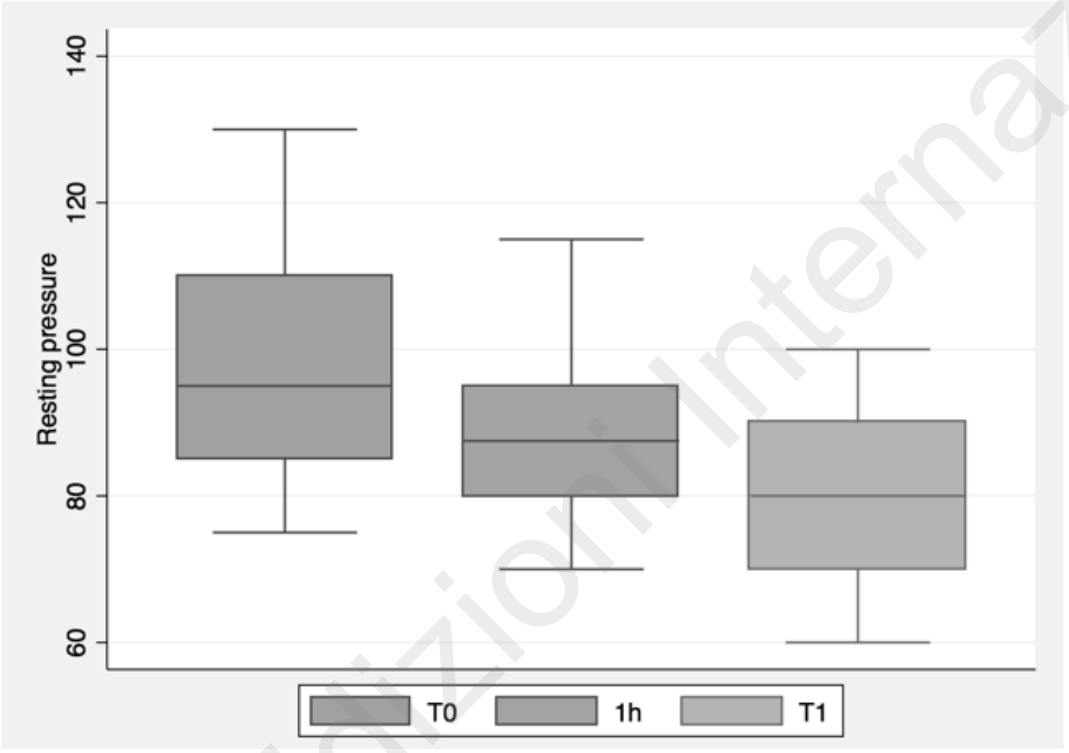


**Figure 2 - Median, IQR range and range of resting anal pressure measured by ARM at each scheduled visit**

exocytosis of ACH; without ACH muscle contraction is blocked. P18 is a modified enkephalin that acts in the same way as endogenous enkephalins which can indirectly close calcium channels. It displaces the binding by G proteins of the encephalin receptors, thus closing the calcium channels, reducing neuron excitability and blocking the release of ACH.

AH8 and P18 have a synergistic effect. In vitro studies have shown that in combination, they inhibit the release of glutamate (an important excitatory neurotransmitter), reducing cell depolarization and consequently the exocytosis of ACH (31, 32).

The supporting tissue of hemorrhoids is regenerated by an oligopeptide derived from Fibronectin that plays a pivotal role in the synthesis of mucopolysaccharides, collagen and elastic fibers (33, 34).

Avenanthramide (Dihydroavenanthramide D) is an active component of oats, and has strong antioxidant, anti-inflammatory and anti-itching properties thus helping relieve symptoms (35-37).

The vanilloid receptor antagonist TRPV1 (transient receptor potential channel vanilloid subfamily member 1) also helps control symptoms, through its involvement in the mechanisms of nociception and itching perception (38, 39).

Finally, Horse chestnut is a botanical derivative (Aesculus Hippocastanum) used for its properties since 1720. The main constituent of the horse-

chestnut is Escin which has marked anti-edema, anti-inflammatory and phlebotonic effect. Studies on animal models and in-vitro studies have shown that Escin reduces the activation and adhesiveness of leukocytes, interferes with the release of inflammatory mediators and the synthesis of prostaglandins and inhibits the activity of elastase and hyaluronidase on the extracellular matrix (40).

In the present set of patients, the synergistic action of all the components of the new ointement produced a significant improvement of signs and symptoms complained, stressing the utility of this topical ally in early stages hemorrhoids, as therapeutic choice, and in more advanced stages as "bridge to surgery" therapy.

## Conclusions

The results of the present study, suggest that topical application of the innovative ointment tested is safe and effective for the management of hemorrhoid symptoms. Its use in early-stage hemorrhoids, during "hemorrhoidal crisis" and in patients with more severe hemorrhoids who are awaiting surgery, promotes quick relief from symptoms. Furthermore, unlike other topical treatments such as glyceryl trinitrate, nifedipine, anesthetics and steroids, it has no adverse effects and could be used also for long-term therapy. The use of an effective topical medication alongside dietary and lifestyle modifications, oral phlebotonics and bulk laxative, which are the fundamentals of conservative therapy for hemorrhoids, could promote a faster symptoms control enhancing the effects of the oral therapy.

Although the type of the study and the small number of patients enrolled are limitation to consider, the encouraging results may provide some evidence which could stimulate further prospective, randomized, controlled trials.

## Acknowledgments

The Authors wish to thank Uniderm Srl for providing the active drug and declare that Uniderm Srl did not have access to the data in the recruitment stage or during the statistical processing and interpretation of the data.

## Compliance with ethical standards

*Conflict of interest*

The Authors declare that they have no conflicts of interest.

*Ethical approval*

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

*Informed consent*

Informed consent was obtained from all individual participants included in the study.

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