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Experimental comparison of properties of natural and synthetic osmotic dilators

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Abstract

Purpose The in vitro study compares natural and synthetic osmotic dilators in selected parameters influencing their clinical efficacy.

Methods Diameters of Laminaria and synthetic dilators (Dilapan-S and Dilasoft) were measured in dry state, during free swelling in isotonic solution and during swelling against a force. Three aspects were evaluated—diameter increase, speed of action and consistency of action.

Results The maximum diameter increase of 3 and 4-mm Dilapan-S was 3.6 and 3.3 times, of Dilasoft 3.2 and 3.1 times, respectively. For Laminaria, it was 2.9 and 2.7 times. The difference between synthetic dilators and Laminaria was statistically significant ($p < 0.01$). Synthetic dilators also swelled faster. Under applied counter force, synthetic dilators increased their diameter more than Laminaria (+3.6 mm for Dilapan-S, +3.8 mm for Dilasoft, +1.2 mm for Laminaria; $p < 0.01$) and achieved faster expansion. Synthetic dilators also showed significantly higher consistency between samples in all experiments.

Conclusions Synthetic dilators compared to Laminaria reached higher maximum diameters, acted faster, were more consistent and were able to expand against force three times more. The results support clinical observations that synthetic dilators are more suitable and preferable for same-day D&E procedure and that fewer synthetic dilators are needed to achieve the same effect.

Keywords Osmotic dilators · Laminaria · Dilapan-S · Dilasoft · Cervical dilation · Cervical priming

Introduction

Many gynecological interventions require cervical canal dilation. The cervix is usually prepared with mechanical or osmotic dilators or with pharmacological methods [1–7]. Osmotic cervical dilators act by absorbing moisture from the surrounding tissue, expanding in size and thus causing mechanical dilation of the cervix. It is believed that the mechanical action is supported by a biophysical mechanism, where the cervical tissue is dehydrated by osmotic action leading to tissue softening [8–11], and by biochemical action, where mechanical pressure induces secretion of prostaglandins, which further contributes to cervix ripening [12, 13].

Currently there are two types of osmotic dilators on the market, which differ by their origin. *Laminaria*, of natural origin, is made from a sea-grown plant of species "Kelp" and contains no synthetic material. *Dilapan-S* and *Dilasoft* are synthetic hydrogel dilators with stem manufactured from an anisotropic xerogel of AQUACRYL [14]. In *Dilasoft,* the material AQUACRYL is water plasticized (i.e. it contains 10–20 % w/w water as opposed to 3.5 % in Dilapan-S), which makes the dilator readily deformable, a feature desired by some physicians, allowing them to facilitate its insertion.

Multiple studies comparing the clinical action of Laminaria and Dilapan-S have been published. Dilapan-S has been reported to have several advantages compared to

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Laminaria. These include mainly faster action, which allows to carry out same-day procedures [8, 15, 16], and higher powerful dilation, which requires the use of about twice less Dilapan-S tents compared to Laminaria [10, 11, 17]. Laminaria's reported disadvantages are also allergic reactions [8, 17] and less predictable effects due to inconsistent shape, dimensions and properties during swelling and expansion process [10, 11, 17]. There have also been case reports of bacteremia following Laminaria placement [17–20]. Due to the risk of infection, clinicians have worried about potential severe infection complications related to Laminaria use [9, 17, 21–23] because bacterial spores can remain in the tents despite sterilization of Laminaria. Laminaria's limitations are largely linked to Laminaria's natural origin and processing without chemical and other modifications, resulting in properties that are solely dependent on the particular portion of the plant from which the dilator is made. The main disadvantage of synthetic dilators is the theoretical possibility of dilator entrapment or fracture, but references in the literature exist only in the form of anecdotal evidence [8].

This paper aims at supporting and explaining some of the clinically observed differences in dilation performance between synthetic dilators and Laminaria with experimental laboratory data that would allow quantifying, evaluating and comparing in vitro properties of the dilators.

Materials and methods

Materials

All experiments were carried out with Dilapan-S (3 × 55 and 4 × 65 mm, MEDICEM Technology, Czech Republic), Dilasoft (3 × 55 and 4 × 65 mm, MEDICEM Technology, Czech Republic), and Laminaria (3 and 4 mm, MedGyn, USA). Isotonic solution (0.9 % w/w sodium chloride aqueous solution in demineralized water) was used as the swelling medium.

Methods

Diameters were measured for 50 samples of each type of dilator, always at three spots of the rods (at both ends and in the middle). Measurements were carried out first in dry state. Then the dilators were placed into isotonic solution at 37 °C and their diameters were measured after 1, 2, 4, 6, 12 and 24 h. Arithmetic mean and standard deviation were calculated for each sample and subsequently each set of samples. The apparatus for measuring swelling against a constant force, Fig. 1, was built from a set of metal blocks Merkur (MERKUR TOYS s.r.o., Czech Republic), a crystallizing dish, two polyamide rollers, textile strap, and a pulley. A

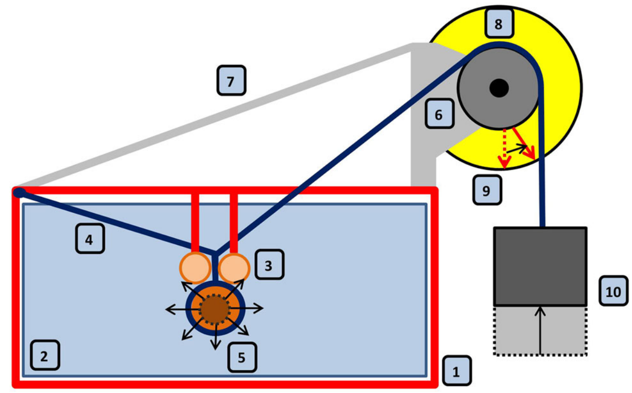

Fig. 1 Schematic drawing of an apparatus for measuring swelling against constant force. *1*—Base made from Merkur blocks, *2*—crystallizing dish with isotonic solution, *3*—two polyamide rollers, *4*—textile strap, *5*—dilatator, *6*—pulley, *7*—arm fixing the pulley, *8*—protractor, *9*—pointer, *10*—weight

dilatator was placed into a loop of textile strap under polyamide rollers. A weight (500 g) was attached to the strap. The apparatus was put into an incubator at 37 °C. The dilator was fully immersed into isotonic solution in a crystallizing dish, which was pre-incubated at 37 °C for 24 h. As the dilator was swelling and its diameter increasing, it was pulling on the textile strap and moving the weight upward by a distance corresponding to the diameter increase. The displacement of the weight was monitored using a protractor and a pointer during 24 h and recorded every 30 min. After the experiment, pieces of the compressed and uncompressed part of the dilator were cut off with scissors and weighed. They were then dried at 105 °C for 24 h and weighed again after cooling down in a desiccator containing activated silica gel, and the water content in both the compressed and uncompressed part was calculated. Five samples of each type of 4-mm dilator were measured.

The data were analyzed using statistical software QC.Expert 3.3. (Trilobyte Statistical Software Ltd., Czech Republic).

Results

The comparison of diameters of 3-mm Dilapan-S, Dilasoft and Laminaria showed that on average, at 24 h, the synthetic dilators swelled to larger diameters than Laminaria, Fig. 2. While Laminaria in our experiments increased its diameter 2.9 times on average, Dilapan-S and Dilasoft increased their diameters 3.6 and 3.2 times, respectively. The described differences were statistically significant ($p < 0.01$). Similar results were reached for 4-mm dilators, when Laminaria increased its diameter 2.7 times on average, and Dilapan-S and Dilasoft 3.3 times and 3.1 times, respectively ($p < 0.01$), see Online resource 1.

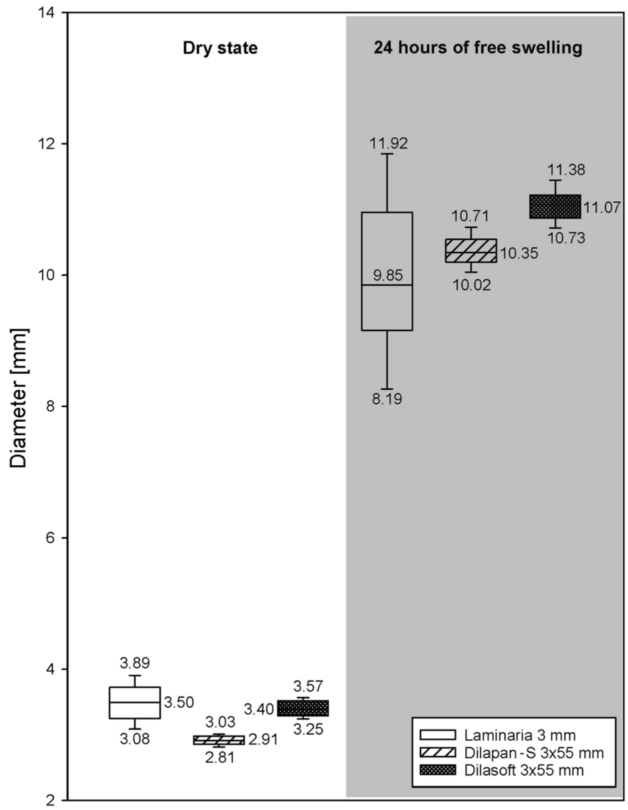

Fig. 2 *Box plot* showing the distribution of average rod diameter for 3-mm dilators for dry rods and rods after 24 h of free swelling in isotonic solution at 37 °C. 50 samples of each type of dilator were measured. Three measurements were made on each sample. The *box* in the *box plot* shows the median and the 25th and 75th percentile of values. The "*T*" graphics show the 10th and 90th percentile of values

Synthetic dilators also exhibited higher consistency among samples, which is graphically shown in the box plots in Fig. 2. Relative standard deviation of diameters (calculated as mean along the length of the rod) of dry dilators was 9 % for Laminaria, 3 % for Dilapan-S and 4 % for Dilasoft. The difference in variance between Laminaria and Dilapan-S and Laminaria and Dilasoft was statistically significant ($p < 0.01$). At 24 h, the difference between Laminaria and synthetic dilators was even greater (14, 3 and 2 %, respectively) and again statistically significant ($p < 0.01$) for both comparisons. The original diameter of 3 mm rods (mean along its length) of Laminaria among the 50 samples measured varied from 2.7 to 4.2 mm, while for Dilapan-S and Dilasoft it ranged only from 2.8 to 3.2 mm, and 3.2 to 3.6 mm, respectively. After 24 h, Laminaria showed a range of 7.2–13.7 mm, while Dilapan-S and Dilasoft diameters ranged from 9.7 to 11.1 mm, and 10.5 to 11.7 mm, respectively.

Synthetic dilators are also more uniform in shape. The diameter measurements at three different spots of the dry rods yielded an average relative standard deviation of 7 % in the case of Laminaria and 1 % in Dilapan-S and Dilasoft. In 3-mm tents, the maximum variation of diameter was 1.4 mm for Laminaria compared to 0.3 mm for synthetic dilators. In the swollen state, the variation of the thickness of the rods was similar—the average relative standard deviation was 6, 1 and 1 %, for Laminaria, Dilapan-S, and Dilasoft, respectively.

These data suggest that although in isolated cases Laminaria can swell more than the synthetic dilators; the average swelling potential is higher for the synthetic dilators, which also exhibit more consistent behavior. Similar data for 4-mm dilators are in Online resource 1.

For clinical use, the speed of dilation is of critical importance. Hence we looked at the speed of diameter increase. As can be seen in Fig. 3, synthetic dilators swell faster than Laminaria. In 4-mm dilators, the same swelling was achieved by synthetic dilators after 4 h and Laminaria after 12 h, while Laminaria never achieved the 6-h diameter of synthetic dilators. The average swelling speed during the first 6 h of swelling was 1.2 mm/h for Dilapan-S and Dilasoft and 1.0 mm/h for Laminaria. Similar results were seen in 3 mm tents, where for the diameter increase synthetic dilators achieve after 6 h, Laminaria needs 24 h (Online resource 1).

During clinical use, the dilators are subjected to a force generated by the cervix. We simulated this situation in experiments where the dilators were swelling against a constant force of 4.9 N (generated by a 500 g weight). This force is in the range of forces exerted by tighter cervices in ex vivo tension experiments reported in the literature [24]. As can be seen in Table 1, Dilapan-S 4 × 65 mm increased its diameter on average almost 3 times more than Laminaria 4 mm, which also resulted in almost 3 times more work done. The variation between different samples was significantly lower for Dilapan-S and Dilasoft than for

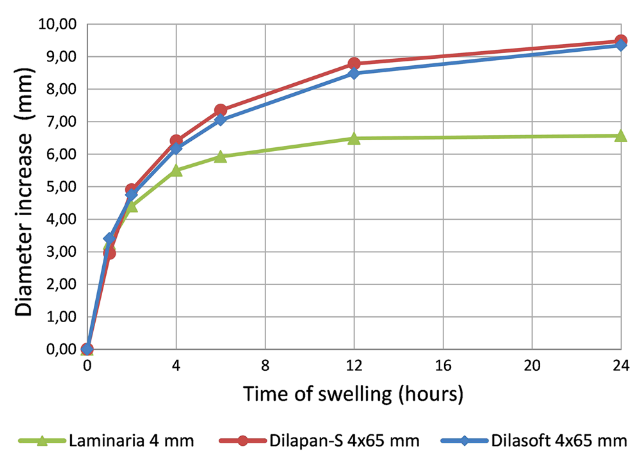

Fig. 3 Average diameter increase of 4-mm dilators as a function of time during free swelling in isotonic solution at 37 °C. Similar figure for 3-mm dilators is in Supporting material S2

Table 1 Diameter increase of dilators subjected to 4.9 N force in isotonic solution at 37 °C for 24 h

	Laminaria 4 mm	Dilapan-S 4 × 65 mm	Dilasoft 4 × 65 mm
Average diameter increase (mm)	1.24	3.58	3.76
Std. deviation (%)	60	10	11
Minimum diameter increase (mm)	0.45	3.05	3.17
Maximum diameter increase (mm)	2.40	4.07	4.18

Five samples of each were measured

Table 2 Water content in dilators under compression and maximum possible water content at 37 °C in equilibrium with isotonic solution

	Laminaria 4 mm	Dilapan-S 4 × 65 mm	Dilasoft 4 × 65 mm
Maximum water content (wt%)	88.4	90.0	88.6
Water content under compression with 4.9 N (wt%)	76.1	85.0	85.5
Unused potential due to compression (%)	14	6	3

Laminaria (RSD of 10 and 11 vs. 60 %). Similar to the experiments without any counter force, it was shown here that selected samples of Laminaria can increase their diameter to almost the same extent as Dilapan-S or Dilasoft, but the wide variation of Laminaria swelling potentials yields relatively low averages compared to the synthetic dilators.

The difference in performance of the synthetic dilators vs. Laminaria is much more significant in experiments with swelling against a force than with free swelling. This is due to the inherent differences in the polymer networks of the natural and synthetic hydrogels in the dilators. Because the polymer network in the hydrogel is stronger, it is capable of exerting a greater pressure on the surroundings and of absorbing more water when pressure is exerted in the opposite direction than the direction of swelling. In other words, greater external pressure is needed to squeeze water out of the gel. It can be seen from Table 2 that compared to Laminaria the synthetic dilators under compression were able to absorb a significantly larger portion of the maximum possible amount of liquid (absorbed without pressure) at the given temperature (37 °C) isotonic solution. This illustrates that the ability of the material to absorb water (i.e. ability to swell), which is in the same range for Laminaria and synthetic dilators (Fig. 2), is not the sole determinant of the effectiveness of the material for dilation. Rather it is a combination of the ability to absorb water and the strength of the polymer network. The latter is much greater in synthetic dilators than in Laminaria.

The dynamics of the dilator swelling against constant force is shown in Fig. 4. The speed of diameter increase of synthetic dilators is on average significantly greater than that of Laminaria. During the first 4 h of swelling, the average swelling speed for Dilapan-S was 0.50 mm/h, for Dilasoft 0.54 mm/h, while for Laminaria it was only

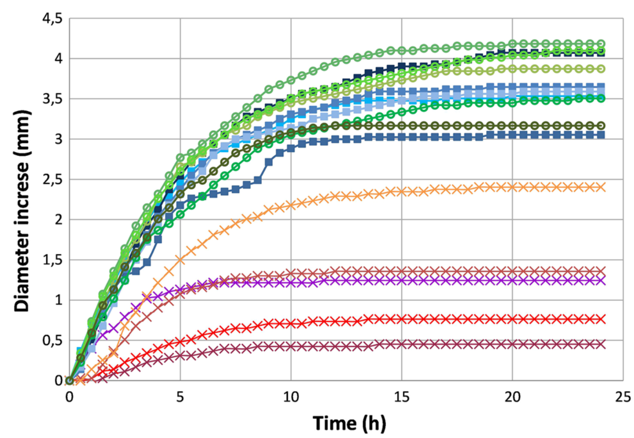

Fig. 4 Diameter increase of 4-mm dilators as a function of time of swelling against force in isotonic solution at 37 °C. *Crosses* are Laminaria, *squares* are Dilapan-S and *circles* are Dilasoft

0.19 mm/h. Some Laminarias collapsed during the first hour of the experiment before they started swelling. On average, Laminaria samples achieved the same diameter after 10 h that Dilapan-S and Dilasoft achieved after 2 h.

Discussion

It has been reported in clinical literature that about twice as many Laminaria tents have to be used for the same procedures as compared to Dilapan-S. For example, Blumenthal [10] in his clinical trial from 1988 observed —"fewer Dilapan devices are needed, which results in less insertion time, less cervical trauma, less patient discomfort, and greater likelihood that all devices will be placed properly in the cervix." These clinical observations are well supported by the in vitro data presented in this paper. Dilapan-S and Dilasoft achieve greater diameter increase both during free swelling and during swelling against a counter force. The difference is more pronounced in the case of swelling against a force, which better simulates the situation in the cervix, than during free swelling (threefold difference vs. 15–25 % increase), because synthetic dilators are purposely made of a stronger synthetic hydrogel AQUACRYL than the naturally occurring hydrogel found in Laminaria.

Clinical observations also point out that unlike Laminaria, Dilapan-S is suitable for same-day procedures, because its effects are faster [8, 16, 25]. These observations are consistent with the dynamics of swelling observed in vitro. In the experiments with counter force, the difference between Laminaria and synthetic dilators was particularly significant, as the same swelling on average was achieved in Laminaria after 10 h and in Dilapan-S and Dilasoft after 2 h. This difference is larger than the difference in clinical observations, which can be explained by a selected counter force, which was at the higher end of the spectrum observed on human cervices [24], by a different geometry of our experiment and by general differences between in vitro and in vivo behavior.

The experiments with counter force, however, clearly do not mimic the situation in vivo, where after 3–4 h of dilation with Dilapan-S, dilation of 10.2 mm was observed in nulliparous women and 11.4 mm in multiparous women [26]. In our experiments with counter force, Dilapan-S diameter after 4 h was only 6 mm. One explanation is that the counter force in vivo is not as strong as in our experiments and likely decreases in time as the cervix dilates. Also, as the synthetic dilator absorbs water from the tissue, the tissue dehydrates and softens, which probably further facilitates dilation. Finally, as suggested previously the mechanical pressure probably induced formation of prostaglandins, which induce cervix ripening [8–11].

Some clinical observations also point out that there is a difference between Laminaria tents and Dilapan-S rods in terms of consistency and predictability of the shape and diameter after their swelling in the cervix [10, 11, 17]. Blumenthal [10, 11] observed shorter induction-abortion time and lower number of devices needed when Dilapan synthetic dilator was used as opposed to Laminaria. Although not as dramatic, a similar difference was observed for Dilapan and Laminaria coated with prostaglandine. Blumenthal speculates that the reasons may involve the more predictable properties of Dilapan compared with Laminaria, particularly in relation to the final diameter of the expanded device and the time required to reach the required size. These observations are in agreement with our results, which show a much greater variability in the final swollen diameter, as well as in the speed of swelling between multiple Laminaria samples compared to Dilapan-S and Dilasoft.

Our in vitro comparison of Laminaria and synthetic dilators shows that synthetic dilators swell to greater diameters and faster than Laminaria and also exert greater forces during swelling. This supports clinical observations that synthetic dilators are more suitable for same-day procedures and that fewer of them are required to achieve the same effect. Our experiments also provide evidence for hypotheses made by clinicians that synthetic dilators have more predictable effects than Laminaria. To confirm the results of the bench experimental study, a prospective randomized clinical in vivo study would be desired that would primarily assess the efficacy of the two types of dilators and also address safety issues such as bacterial colonization over time, migration to the uterine cavity and possible fragmentation.

In addition, it would be interesting to find out why Laminaria tents differ so much one from another and whether a better selection of tents could lead to more predictable results. We observed that darker rods swell better against counter force than lighter ones, but we examined too few samples to make unequivocal conclusions. It is known that the chemical composition of Laminaria vary with environmental conditions, maturity, gender and even season [27] and it is, therefore, likely that all these factors influence its properties.

It would also be interesting to study the difference in ripening effect in vivo between Laminaria and synthetic dilators. Since it has been experimentally shown that mechanical stress produces biochemical ripening-like changes in uterine cervical fibroblasts cells [28], in theory, synthetic dilators with greater force exerted on the cervical cells should produce more ripening. In addition, due to their higher propensity for water, they should dehydrate the surrounding tissue more than Laminaria. Assessment of water content of the cervical tissue, the content of prostaglandins and other biochemical agents linked to cervix ripening together with dilation extent could yield the much needed information.

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Conflict of interest The authors are affiliated with an R&D company MEDICEM Institute s.r.o., Czech Republic, which is a sister company of MEDICEM Technology s.r.o., Czech Republic, the legal manufacturer of Dilapan-S and Dilasoft. The authors declare that the results presented in this paper are based on sound scientific methods and analyses. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

Ethical standards The manuscript does not contain clinical studies or patient data.

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