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A real-world evaluation of an herbal treatment for infantile colic reported by 1218 parents in Israel

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ABSTRACT

Purpose: Infantile colic (IC) or fussing and crying behavior of unknown cause, affects up to 20% of the infant population and is one of the major reasons for parents to seek medical advice. Therapeutic options are limited and the key component for IC management is parental support. Fennel-based herbal treatments were shown to significantly reduce crying time. The current study was designed to evaluate the parent perception of effectiveness of a fennel-based commercially-available herbal treatment for IC (BabyCalm, Hisunit Ltd., Israel) using a retrospective online survey.

Design and methods: This was a real-world observational, case-control retrospective study. Parents of babies with IC symptoms, who either used the herbal product for their baby or did not use any product were invited to participate in an online survey during August–December 2019. The primary outcome was the perceived level of treatment success and symptom improvement.

Results: 1218 parents of IC babies (48% females, 90% up to 3 months of age, 58% exclusively breast-fed) responded to the survey of whom 771 used the treatment. Significantly fewer IC-related symptoms were reported by parents who used the product compared to those that did not. Parents perceived the treatment as successful in 65% of the cases, reporting meaningful improvements within 30 min for 69%–79% of the symptoms.

Conclusions: The majority of parents perceived the herbal treatment as effective in rapid symptom reduction suggesting that this may provide a satisfactory solution for IC in the community.

Introduction

Infantile colic (IC) is one of the most commonly encountered problems within the first 3 months of a baby's life, affecting up to 20% of infants, and is one of the major reasons for parents to seek medical advice (Benninga et al., 2016; Lucassen et al., 2001). It is characterized by excessive, inconsolable crying that can last 3 or more hours per day, and causes significant distress to parents, potentially resulting in anxiety, risk of child abuse, as well as economic costs (P. Lucassen, 2010).

According to Johnson et al. (Johnson et al., 2015), the key components for the management of colic from the pediatrician's point of view are parental support and reassurance that this condition is normal and will most probably pass by 3–6 months of age. However, parents who witness their baby crying inconsolably for hours every day are understandably frustrated by this approach, and seek over-the-counter non-prescription alternatives.

Herbal medicines for the treatment of IC symptoms are sold worldwide in pharmacies as over-the-counter remedies (Joubert et al., 2008; Mahomoodally & Sreekeesoon, 2014; Oshikoya et al., 2009). Babycalm (Hisunit Ltd., Israel) is a herbal product sold over-the-counter, that is used in Israel, Europe, Russia, and China by parents for the management of colic, as well as gas, reflux, and other gastrointestinal problems in infants, with no reported adverse events. The three active ingredients in the product are fennel (*Foeniculum vulgare*), anise (*Pimpinella anisum L.*), and mint (*Mentha piperita L*) that have been shown to have direct beneficial effect on gastrointestinal disturbances (Alexandrovich, Rakovitskaya, Kolmo, Sidorova, & Shushunov, 2003; Alves, de Brito Rde, & Cavalcanti, 2012; Amato, Liotta, & Mule,

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2014; Badgujar, Patel, & Bandivdekar, 2014; Mosaffa-Jahromi, Lankarani, Pasalar, Afsharypuor, & Tamaddon, 2016; Savino, Cresi, Castagno, Silvestro, & Oggero, 2005; European Medicine Agency EMA Mint, 2020; European Medicine Agency EMA Fennel, 2007; European Medicine Agency EMA Anise, 2012).

Infantile colic diagnosis is based on the full Wessel or Rome III criteria (i.e. crying >3 h a day, >3 days a week, for >3 weeks). However, a large survey in the UK (M. Goldman & Beaumont, 2017) found that fewer than 1% of the babies in the community who were treated with a prescription drug specific for IC filled these criteria. These findings imply that babies that participated in IC clinical studies have the most severe IC symptoms, and clearly do not represent what parents or pediatricians in the community perceive as IC. Since products for treatment of IC are targeted to infants in the community, testing treatments on the most severe cases may undermine the beneficial effects that would otherwise be detected.

Thus, this study was designed to gather real-world parents' perception of the effectiveness of the herbal product for the treatment of IC in the community, and to compare the population characteristics of infants given this treatment to those who did not receive any treatment.

Methods

Overview

We report here on a real-world, observational, retrospective, case-control study. Parents of babies with IC were invited to participate in an online survey. The data gathered pertained to babies with IC who were treated by their parents with Babycalm ('Treated') or not treated with any product ('Control'). The survey was distributed using the online Survey Monkey platform (SurveyMonkey Inc., San Mateo, California, USA.). Data were gathered automatically. Analysis was performed by a third party not affiliated with the manufacturer. The design and report followed the guidelines for reporting medical surveys outlined by Artino et al. (Artino Jr., Durning and Sklar, 2018).

Ethical statement

The survey was anonymous and therefore the ethical committee waived the requirement for informed consent (Maccabi Health Services #0019-19-MHS).

Participants and setting

Between August 2019 and December 2019, parents of babies with IC (past and present) were invited to participate in an online survey. Responders were offered a portable wet wipe pouch (worth approximately $10) as an incentive to complete the survey. The invitation was posted on social media and relevant internet sites, and physically posted at pediatric clinics. There were no restrictions regarding the feeding method or age. Inclusion criteria: parents reported that babies had IC and exhibited at least one of the following symptoms: 1) cried>3 h a day; 2) cried>3 days a week; 3) cried>3 weeks sequentially; 4) squirmed in apparent pain or discomfort while crying; 5) clenched fists while crying; 6) drew knees to tummy or arched back while crying. Exclusion criteria: 1) other treatment modalities used alone or in combination with Babycalm; 2) use of a medicine that may have influenced colic symptoms, such as reflux drugs; 3) maternal diet change during treatment.

Survey design and questions

The survey items were based on Goldman et al. (M. Goldman & Beaumont, 2017) as well as a review of symptoms and experimental findings pertaining to IC according to the medical literature and clinical study databases. A group of experts including two community pediatricians and two scientists identified relevant data items and outcomes. The survey was in Hebrew. A pilot test for clarity and accuracy of items was conducted with a group of 15 parents, and the version was finalized accordingly. The survey comprised 23 closed-ended single and multiple-choice questions and a few open-ended response questions. The first section was not specific to the treatment modality and included questions regarding where the questionnaire was seen, demographics (baby sex, age, method of feeding, birth order), and colic diagnosis (who diagnosed colic, what symptoms/signs were used to diagnose colic, time of appearance of symptoms). The second section was specific to parents who used the herbal product and referred to the manner of use (when/for how long the product was used, dose used [less than recommended, as recommended, more than recommended]) and treatment effectiveness (success, symptom improvement). The third section referred to concomitant health conditions characteristic to babies of this age. A translated version of the survey is provided as supplemental material.

Study outcomes

Overall treatment success was graded as: 1 = yes – completely resolved the problem, 2 = yes – favorable effect on the symptoms, 3 = helped a bit, 4 = did not solve the problem, 5 = not sure. This measure was dichotomized into 1 = successful (possibilities 1 or 2) or 0 = not successful (possibilities 3–5). Symptom improvement was graded with a 7-point Likert scale (completely stopped, dramatic, significant, apparent, more than slight, slight, none or worse). Time to achieve the effect was: immediate, up to 30 min, 30 min-2 h, 2–24 h, 1–2 days, 3 days or more, symptoms were not relieved. To rule out detrimental effects of the product in the community, the incidence of common infant health conditions requiring a visit to the pediatrician and hospitalization rate of the treated were compared to that of the controls.

Statistical analysis

Sample size was calculated using PASS-15.0.4 software (NCSS Statistical Software, Kaysville, UT). The number of live births in Israel updated to 2017 was 183,648 (Israel Central Bureau of Statistics, 2018), and the incidence of IC is 17% (P. Lucassen, 2010), hence the expected number of babies with IC per year is 31,220. The minimum sample size was determined to be 380 responders from each group estimated at 95% confidence interval and a margin of error of 5%.

Data were summarized in counts and percent. Responses of multiple-choice questions were presented in Pareto graphs. Comparison between groups was conducted by Chi-square test, using Holm-Bonferroni sequential correction for multiple comparisons. The relationship of order of birth with incidence of use was tested with Spearman's (non-parametric) correlation test. Independent predictors of the dichotomized treatment success were derived using a logistic regression full model fit. $p < 0.05$ was considered significant. Statistical analyses were performed with SYSTAT, version 13.2 (Systat Software, Chicago, IL).

Results

Accountability

Responses of 1550 parents were received, of which 332 were excluded: 93 were found ineligible because they reported that their baby did not have colic ($n = 3$) or colic-related symptoms ($n = 90$), and 239 reported using products or treatment modalities other than Babycalm. The remaining 1218 responders included 447 responders who reported not using any product and 771 responders who used Babycalm. Finally, 10 responders were not included in the effectiveness analysis due to missing information pertaining to improvement. The

CONSORT diagram of the study flow is provided as supplemental material.

Demographics and feeding method

Overall, the incidence of IC was similar in males and females ($p = 0.58$) and the majority (>85%) of the babies were diagnosed up to 3 months of age. Significantly more babies who were treated were bottle-fed, while significantly more babies who were not treated were breast-fed ($p < 0.001$ for both). As the order of birth increased, the incidence of use decreased in the treated babies ($r = -0.241$, $p < 0.001$ by Spearman correlation), with a two-fold increase in firstborns of those treated vs. untreated (41% vs. 21%) (Table 1).

Colic diagnosis and symptoms

IC symptoms were reported to appear throughout the entire day, after meals, in the early evening, or late in the evening and persisting until dawn (32%, 29%, 32%, and 24%, respectively). Overall, the diagnosis was based in 76% of the cases on symptoms of discomfort while crying including squirming in apparent pain or discomfort, drawing knees to the tummy, arching the back, or clenching fists. In contrast, full Wessel criteria were reported in only 3.4% of the babies. It should be noted that diagnosis was done by parents in 87% of the cases and by pediatricians (physician or pediatric nurse) in only 14% of the cases. Nevertheless, full Wessel criteria were reported in only 6.6% of the babies who were taken to a pediatrician for diagnosis (11 of 166). Interestingly, babies who did not receive treatment presented with relatively more symptoms compared to those who were given treatment (Fig. 1), reaching significant separation for squirming in apparent pain (treated vs. control: 56% vs. 65%, $p = 0.005$), clenching fists (16% vs. 23%, $p = 0.003$), and crying >3 days a week (8% vs. 13%, $p = 0.04$).

Treatment effectiveness

Treatment was considered successful by 65% (493 of 761) of the parents, of whom 13.4% reported 'complete resolution' and 51.4% reported 'favorable effects on the symptoms'. Another 28% of the parents reported that the treatment 'helped a bit', while the remaining 7.2% of the parents were either 'not sure' or reported that the treatment 'did not solve the problem'. The success of the treatment was found to be significantly associated with the dose of administration and feeding method, but not with sex, order of birth, or age (Table 2). Specifically, administering a less than recommended dose or exclusively breast-feeding were associated with an unsuccessful treatment outcome (Table 2). Meaningful improvement of symptoms ('apparent' improvement up to 'completely stopped') was reported in 69%–79% of the cases, with 'dramatic' to 'completely stopped' reported in 26%–34% of the cases (Fig. 2). The beneficial effect was noted within 30 min by 72% ($n = 541$) of the parents, and by 2 h by 86% ($n = 645$) of the parents.

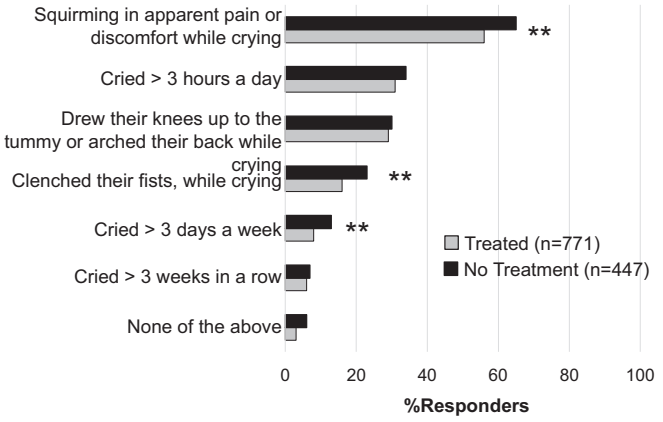

Fig. 1. Symptoms of Infantile Colic.
Pareto graph showing the prevalence of reported IC symptoms in babies who were treated with Babycalm vs. those who were not treated as percent of responders. Note significantly less symptoms reported by parents who administered the fennel-based treatment to their babies. **p < 0.001 by Chi-square.

Common health conditions

The incidence of constipation and diarrhea, for which parents consulted with a pediatrician, was significantly lower in babies treated with the herbal product compared to those not treated with any product (Treated[$n = 743$] vs Control[$n = 433$]: constipation 5.1%-vs-9.9% and diarrhea 1.2%-vs-4.4%, $p = 0.002$ and $p = 0.001$ respectively by Chi-square). The incidence of other common health conditions was not significantly different between treated and untreated babies (pharyngitis 0.4%-vs-0.7%, high fever 1.1%-vs-2.1%, pneumonia 1.5%-vs-0.7%, and cyclic vomiting 3.9%-vs-3.7%, all $p > 0.16$).

Discussion

This study was designed to evaluate the effectiveness of a commercial herbal product for the treatment of infantile colic (IC) in a real-world population. Using an internet survey distributed through social media, responses from 1218 parents of infants who had IC and either used the product ($n = 771$) or did not use any product ($n = 447$) were gathered automatically and analyzed by a third party unaffiliated with the manufacturer. Parents perceived the treatment as successful in 65% of the cases, reporting meaningful improvements within

Table 1
Demographics, Feeding Method, Age, Order of Birth.

Variable	No Treatment (n = 447)	Babycalm (n = 771)	p
Sex* Female:Male (%Female)	224:223 (50%)	366:405 (47%)	0.37
Age at diagnosis*			
Up to 1 month	170 (40%)	351 (46%)	0.011(0.033)
1–3 months	206 (46%)	363 (47%)	0.740
3–6 months	54 (12%)	45 (6%)	<0.001
>6 months	10 (2%)	12 (2%)	0.389
Feeding method*			
Breast-fed	306 (68%)	402 (52%)	<0.001
Bottle-fed	31 (7%)	155 (20%)	<0.001
Combination	110 (25%)	214 (28%)	0.230
Order of birth**			
1st	93 (21%)	312 (41%)	r = −0.241
2nd	96 (22%)	171 (22%)	p < 0.001
3rd	89 (20%)	139 (18%)	
4th	54 (12%)	59 (8%)	
5th or more	115 (26%)	90 (12%)	

* by Chi-square with Holm-Bonferroni sequential correction for multiple comparisons;
** by Spearman's correlation.

Table 2
Predictors of Treatment Success by Logistic Regression.

Predictor	Odds Ratio	p*	95%CI
Dose of use: less than recommended	0.51	<0.001	0.36, 0.73
Feeding method: breast-fed	0.69	0.040	0.48, 0.98
Feeding method: bottle-fed	1.06	0.802	0.67, 1.68
Order of birth	1.03	0.599	0.92, 1.15
Age at diagnosis	1.09	0.465	0.97, 1.37
Sex: female	1.19	0.259	0.88, 1.61

* by logistic regression full model fit with dichotomized success as the dependent variable.

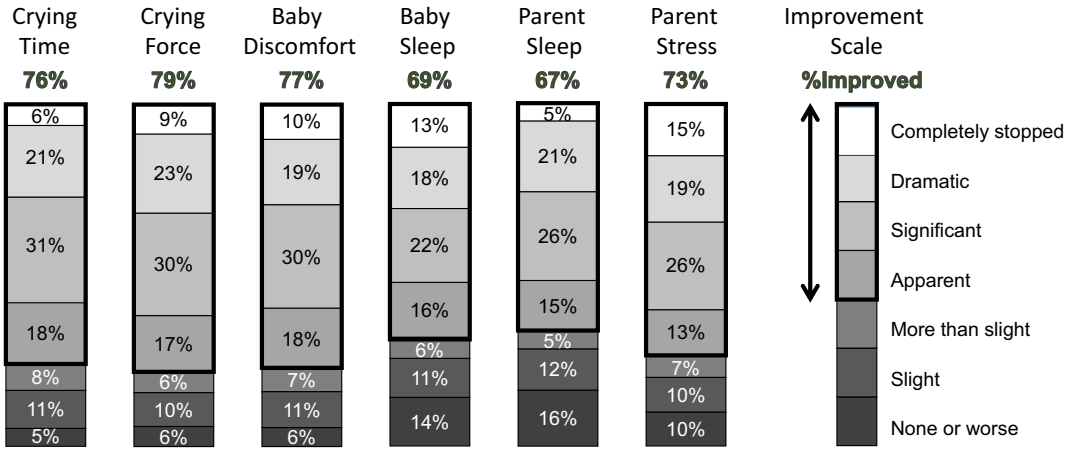

Fig. 2. Infantile Colic Symptom Improvement.
Stacked bar graph showing the distribution of improvement level for each symptom as graded by the parents according to the improvement scale presented on the right. Overall %improvement = the summed percentage of the four highest improvement categories from 'apparent improvement' to 'completely stopped'.

30 min of administration for approximately 70% of the symptoms including crying time, crying force, baby discomfort, baby sleep, as well as parent stress and sleep. In addition, significantly fewer IC-related symptoms and significantly fewer gastrointestinal health conditions requiring a visit to the pediatrician were reported by parents who used the treatment compared to those who did not use any product.

The rate and time of meaningful symptom improvement found in this study (69%–79% of the cases within 30 min) was similar to the 69.7% rate of improvement within 1 day reported by Goldman et al. who evaluated the perceived effect of the pharmacological treatment simethicone for IC, also using a survey tool (M. Goldman & Beaumont, 2017). It should be noted that simethicone failed to show superiority in placebo-controlled studies in which babies were recruited only according Wessel criteria (Danielsson & Hwang, 1985; Metcalf et al., 1994).

According to a Cochrane review, there is low- to moderate-quality evidence that herbal agents reduce the duration of crying episodes with different magnitudes of benefit noted across studies (Biagioli et al., 2016). Specifically, for the active ingredients in this herbal product, essential oil of fennel has been shown to regulate the motility of the intestinal smooth muscles and to reduce intestinal gas, and was shown to significantly reduce crying time compared to placebo in two randomized placebo-controlled clinical studies that included a total of 218 babies (Alexandrovich, Rakovitskaya, Kolmo, Sidorova, & Shushunov, 2003; Badgujar, Patel, & Bandivdekar, 2014; Savino, Cresi, Castagno, Silvestro, & Oggero, 2005; European Medicine Agency EMA Fennel, 2007). Anise is a traditional herbal medicinal product used for symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating and flatulence. Anise was found to be significantly superior in improving irritable bowel syndrome symptoms over placebo or an active drug (Colpermin) in a double-blind clinical study including 120 adult patients ((Mosaffa-Jahromi, Lankarani, Pasalar, Afsharypuor, & Tamaddon, 2016; European Medicine Agency EMA Anise, 2012). Mint (peppermint) oil was found to have a dose-related antispasmodic effect on the smooth musculature (Amato et al., 2014). Mint was compared to simethicone in a small double-blind crossover study in 30 babies with IC and no difference was found in crying duration or number of crying episodes (Alves, de Brito Rde, & Cavalcanti, 2012; European Medicine Agency EMA Mint, 2020).

This is the largest survey published in the medical literature of IC babies in this region to date. Based on the data gathered, we found that similar to other geographical locations, IC afflicts males and females equally and appears mostly up to 3 months of age (Clifford et al., 2002; Leung & Lemay, 2004; Wolke et al., 2017). Although IC is considered an 'evening colic' because of its characteristic circadian rhythm of pain in the early evening (Illingworth, 1985), in this survey, parents reported that IC appeared at all times of the day. Diagnosis was mostly done by parents of whom only 14% visited a pediatrician for a formal diagnosis – similar to the rate reported in the literature for a consultation with a healthcare worker for the problem of excessive crying (Wade & Kilgour, 2001). An important finding of this study was that only 6.6% of the babies diagnosed with IC by a pediatrician and 3.4% overall were reported to manifest full Wessel criteria that are used in clinical studies as inclusion criteria. This mirrors the findings by Goldman et al. (M. Goldman & Beaumont, 2017) who reported that only 13 of 4004 babies (<1%) who were treated with prescription drugs for IC exhibited full Wessel criteria.

Practice Implications

The clinical community is looking for IC treatments that have been validated in clinical trials to provide evidenced-based recommendations. However, to date, systematic evaluations of published clinical trials of pharmacological agents, probiotics, nutritional modification (dietary changes), and massage have concluded that these have limited effectiveness in reducing crying episodes and severity of IC symptoms (Biagioli et al., 2016; Hall et al., 2012; P. Lucassen, 2010; Shirazinia et al., 2021). Dicyclomine hydrochloride was found to have beneficial effects, but was not recommended due to a high incidence of side effects (Goldman, 2004). Certain strains of probiotics were found effective when given to breast-fed infants (Harb et al., 2016; Shirazinia et al., 2021), but not all parents are willing to give their babies probiotics (Andersen et al., 2018; Bridgman et al., 2014), and not all babies are breast-fed. On the other hand, herbal medicines for the treatment of IC symptoms are sold worldwide in pharmacies as over-the-counter remedies (Joubert et al., 2008; Mahomoodally & Sreekeesoon, 2014; Oshikoya et al., 2009) and herbal components are the basis of many traditional remedies for IC (Bagherian et al., 2021). Parents perceive herbal treatments as 'natural' and 'safe'(Arabiat et al., 2019). Practically, this approach, together with the findings from this large survey, allow the use of the product to be considered by parents who experience colic in their children, in whom manifestation is less severe. Babies who have infantile colic have the right to have satisfactory pain management that has been proven to be effective and reduces the suffering not only of babies, but also of their parents.

Limitations

The strength of this study is derived from the lack of restrictions on feeding method, age at diagnosis, or method of diagnosis. The data were gathered automatically and the researchers had no influence over the

exposure because the parent chose whether or not to treat the IC. Moreover, in view of the large size of the study population, it was possible to evaluate potential effects on the incidence of common health issues of this product compared to the controls, which is largely restricted in clinical studies because of the limited sample size, particularly in this age group.

The limitation of the study stems from its retrospective design and biases that are characteristic to cross-sectional online surveys and surveys in general. Selection bias towards those who are more active online was not a prominent obstacle in this study because this survey was targeted to parents in an age group that is very active online. Moreover, the recruitment was done by snowballing in which the link to the survey was copied anonymously to a variety of parent Facebook pages (probably because of the small incentive given). Indeed, >90% of the responders originated from sites that were not linked to the company site. Regarding response bias, since this was an anonymous survey, we did not gather information on the parents themselves. However, validity of the survey results was demonstrated by the fact that certain characteristics of the babies, including method of feeding and age of the babies with colic are in accordance with data from the region (Ophir, 2018; US National Immunization Surveys, 2020). When planning the survey, we used neutrally worded questions without leading questions and answers, in order to avoid untruthful response. To avoid order bias, we grouped the questions by topic, and included a minimal set of questions to shorten the time required to fill out the survey. Finally, to enhance the validity of the survey questions, we involved experts in survey construction and conducted a pilot survey before the final phrasing was decided upon.

Conclusions

In summary, in this large cross-sectional survey, we evaluated the effectiveness of Babycalm, an herbal treatment sold over-the-counter and based on a combination of fennel, anise, and mint. According to reports by 1218 parents with babies suffering from infantile colic, of whom 771 used the product and 447 did not use any treatment, the product was perceived as successful in 65% of the cases, with a 70% meaningful improvement across all characteristic symptoms. Colicky babies in the community have significantly reduced symptoms compared to those participating in clinical studies. This herbal treatment may provide a satisfactory solution for the less severe manifestation of IC that is predominant in the community thereby alleviating the suffering of both infants and their stressed-out parents in this critical period of life.

Conflicts of interest and source of funding

Drs. Gavish and Maor were paid as scientific consultants by the manufacturer of the product. All other authors declare no conflicts of interest relevant to this article. The manufacturer of the product covered the cost of the incentive for parents to respond to the survey and paid for the statistical analysis of the data. The manufacturer was not involved in the study design, data collection (automatic), data analysis or interpretation, or writing of the report.

Data sharing statement

*Deidentified individual participant data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Dr. Lilach Gavish (*lilachg@ekmd.huji.ac.il*).*

Author contribution

Dr. Gavish contributed to the conception and design of the study, coordinated the data collection, conducted the data analysis, and drafted the initial manuscript.

Dr. Maor contributed to the conception and design of the study and the interpretation of the data.

Dr. Korchia contributed to the conception and design of the study, was responsible for the development of the survey tool and the interpretation of the data.

Dr. Cohen contributed to the development of the survey tool, was part of the initial data analysis, and contributed to the interpretation of the data.

All authors critically reviewed the manuscript for important intellectual content, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Drs. Gavish and Maor were paid as scientific consultants by the manufacturer of the product. All other authors declare no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedn.2022.12.002.

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