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ORIGINAL ARTICLE

Conservative treatment in uncomplicated acute appendicitis: reassessment of practice safety

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Abstract The success rate of conservative treatment for children with uncomplicated appendicitis was prospectively evaluated among 197 children. All who received intravenous antibiotics for 3–5 days, and if symptoms resolved, were discharged home on oral antibiotics for 5 days. Failure rate, symptoms, laboratory signs, and sonographic findings were evaluated for prognostic markers of treatment failure. Children were followed for 18 months. The success rate of conservative treatment was 87%, with shorter hospital stays compared to children who eventually needed surgery (72 [60–84] vs. 84 h [72–126], $P = 0.001$). Vomiting and/or nausea and intraluminal fluid on sonography were the only prognostic signs of failed treatment ($P = 0.028$ and $P = 0.0001$, respectively). After multi-regression analysis, intraluminal fluid was the only prognostic sign for failed treatment (odds ratio = 10.2; 95% CI 3.3–31.8, $P = 0.001$). Patients who failed conservative treatment were successfully operated without significant morbidity. Pathology findings were compatible with acute or subacute inflammation in 94% of operated AA, with no perforated appendices.

Conclusion: When applying rigorous criteria for children with uncomplicated appendicitis, a high success rate can be achieved with conservative treatment. Those who fail conservative treatment have a benign medical course without serious complications. Intraluminal fluid may increase risk for conservative treatment failure.

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What is Known:

- *Conservative treatment in uncomplicated acute appendicitis is a reasonable alternative to appendectomy.*

What is New:

- *Using rigorous criteria for conservative treatment in uncomplicated acute appendicitis is safe and feasible.*
- *Intraluminal fluid should be considered a contraindication to conservative treatment.*

Keywords Acute appendicitis · Children · Conservative treatment · Intraluminal fluid · Appendectomy

Abbreviations

AA	Acute appendicitis
ILF	Intraluminal fluid
US	Ultrasound

Introduction

Acute appendicitis (AA) is a common medical condition in children [11], and appendectomy has been the treatment of choice. Recently, several observational studies [1, 8, 12, 20, 21], including one study from our group [20] evaluated conservative treatment with an antibiotics as a first strategy for uncomplicated appendicitis in children and showed that most patients in the "antibiotics-first" group were able to avoid appendectomy. These studies used varying criteria to trigger a crossover to surgery, which ranged from 0 to 37% [21]. This wide range suggests substantial heterogeneity of indications for conservative treatment.

In the current study, we prospectively tested our "antibiotics first" strategy among a much larger population with an established diagnosis of uncomplicated appendicitis. Our hypothesis was that the indications for conservative treatment of AA in children would be safe, and that appendectomy would be avoided in the majority of patients.

Methods

The study was approved by the Institutional Review Board of Meir Medical Center, Kfar Saba, Israel, and was conducted from October 2013 to February 2016. This non-randomized, prospective study included all children with clinical, laboratory, and radiological findings suspicious for uncomplicated AA. None of the children who participated in our pilot study [20] also participated in the current study. All children who presented to the hospital's emergency department with a clinical suspicion of acute appendicitis were evaluated for AA using abdominal ultrasound (US) and laboratory findings. The Pediatric Appendicitis Score reported by Samuel [17] was assessed in all patients. This score assigns 2 points for cough/percussion/hopping tenderness in the right lower quadrant of the abdomen; 2 points for tenderness over the right iliac fossa; and 1 point each for anorexia, pyrexia, nausea/vomiting, leukocytosis, polymorphonuclear neutrophilia, and migration of pain. The maximum total score is 10, and a score ≥7 is strongly suspicious for acute appendicitis. All patients included in this study had a score ≥7. Recurrent appendicitis was diagnosed using the same criteria as the initial episode. Appendicitis was further confirmed by US showing signs of appendicitis if the appendix measured more than 6 mm of maximum outer diameter in transverse section and inflammatory changes such as increased echogenicity of peri-appendiceal fat, appendiceal wall hyperemia or thickening, and/or peri-appendiceal fluid. The presence of appendiceal intraluminal fluid (ILF) was also evaluated as a possible useful additional finding. US exams were considered positive for complicated appendicitis if there were marked inflammatory changes in the right lower quadrant with or without visualization of the appendix or fluid collection indicating peritonitis or abscess. Based on our previous experience of gangrenous changes [20], children in whom US detected an appendicolith were not eligible for conservative treatment. If none of these findings (i.e., signs of complicated or uncomplicated AA) were observed on US, appendicitis was not diagnosed and other causes of abdominal pain were considered. All patients who met the diagnostic criteria of acute uncomplicated, non-perforated appendicitis and were eligible for conservative management with antibiotic therapy during the study period were included. Exclusion criteria for conservative management based on our previous experience [20] included one or more of the following: symptoms for more than 24-h duration; diffuse tenderness; signs of complicated appendicitis on US or peri-appendicular abscess; significant comorbidities such as heart anomalies, immune deficiencies, inability (or unwillingness) to complete 3–5 days of intravenous antibiotics; and inability to return to the hospital in a timely fashion if symptoms recurred or persisted.

The study participants and their parents were informed of the potential advantages and disadvantages of operative and conservative management, including discussion of the current uncertainty regarding the optimal management of such cases. After these explanations, the final decision was left to the child's parents. Consent for inclusion in the study, which comprised a prospective chart review, was obtained from the parents. Intravenous (IV) ceftriaxone (50 mg/kg/day) and IV metronidazole (30 mg/kg/day) were started. In the presence of amelioration of clinical signs and symptoms, surgery was delayed and IV antibiotics were given for 3–5 days. Once asymptomatic after 3–5 days of IV antibiotics (e.g., normal temperature and WBC, no abdominal tenderness or vomiting), the surgery was canceled and the children were discharged home on oral amoxicillin and clavulanic acid (50 mg/kg/day) for an additional 5 days. Criteria for discharge were established a priori and were as follows: afebrile for 48 h, on oral antibiotics, adequate pain relief on oral analgesia, tolerating regular diet, and mobile. In the event of no response to conservative management within 24–48 h or aggravation of any of the clinical signs, appendectomy was advised.

After being discharged, parents received a phone call within 48 h inquiring about the child's overall clinical condition. They were told that any symptoms suspicious of AA should be followed by a telephone call to the Pediatric Surgery Department to consult regarding further necessary steps of care. Those who were admitted within the 18-month follow-up period with signs, symptoms, and US confirmation of AA were analyzed for symptoms and signs of complicated or uncomplicated AA, and the same criteria as for the first AA event were reapplied. Cases of complicated AA were operated immediately and uncomplicated AA meeting the inclusion criteria were managed conservatively. All children undergoing surgery had either a laparoscopic appendectomy with a three-

port technique or open appendectomy, decided by the attending surgeon. Per our protocol, no difference in length of hospitalization or antibiotic treatment was carried out in relation to the surgery technique. Appendix specimens were analyzed for signs of infection, inflammation, and perforation. Data collection included symptoms, US findings compatible with AA and pathology results.

The primary outcome of this study was the success rate of our conservative treatment defined as a child with the diagnosis of uncomplicated AA, undergoing only medical treatment with no need for appendectomy within hospitalization or follow-up period. Our secondary outcomes included length of hospitalization and antibiotic treatment and pathology results of children who failed conservative treatment.

Statistical analysis

All data were analyzed using SPSS software version 21 (SPSS, IBM, Somers, NY, USA). Descriptive statistics such as mean, standard deviation, median, and percentiles were used for all variables. Kolmogorov-Smirnov test was used for assessing normal distribution for the quantitative parameters. The Mann-Whitney U test was used to evaluate differences between two groups in cases where normality was not assumed; otherwise, the *T* test was used. Fisher's exact test was used to determine differences between categorical parameters. A receiver operating characteristic (ROC) curve was constructed to describe the relationship between the sensitivity and the specificity of different parameters in identifying children at risk for failed conservative treatment. After comparing study parameters in univariate analysis, a multivariate logistic regression model was used to predict children who are at risk for failed conservative treatment. $P < 0.05$ was considered significant.

Power analysis: Sample size calculation was based on the following assumptions: alpha = 0.05, 95% confidence level, and 85% success rate for conservative treatment. This required at least 193 patients. This sample size means that 95% of the time, the study would find that 80 to 90% of the children with uncomplicated AA would be managed successfully with non-operative conservative treatment.

Results

A flow diagram of the diagnosis and management of children who were treated for AA during the study period is shown in Fig. 1. Eligible for the study were 197 patients who were diagnosed with uncomplicated AA and fulfilled the entry criteria. Overall, 26 children failed conservative treatment and needed surgery, 14 underwent laparoscopic appendectomy and 12 open appendectomy, 10 within the first hospitalization (median 3 days, IQR 2–4 days) and another 16 children within the follow-up period (median 87 days, IQR 21–211 days). Table 1 presents the demographics and initial characteristics of those who were successfully treated conservatively and those who failed conservative treatment and needed surgery. No significant difference was noted between the groups except for the occurrence of vomiting, which was more common in the failed conservative treatment group. The length of hospital stay for operative treatment was longer than for conservative treatment. However, no difference in length of hospitalization between first conservative and subsequent conservative treatments was noted (68 [51–79] vs. 75 h [63–107], respectively, $P = 0.42$). The operative time and length of hospital stay for operative treatment at the time of recurrence after the first successful non-operative treatment were equivalent to those for operative treatment at the time of initial diagnosis (79 [58–81] vs. 84 h [72–126], $P = 0.59$). The length of antibiotic treatment (intravenous and oral) in the conservative treatment group was longer than that for the operative treatment group (Table 1).

Comparing US findings between the two groups showed no difference except for ILF which was more common in the failed conservative treatment group (Table 2).

ROC curve analysis of children's age, duration of abdominal pain, CRP serum levels, and US appendiceal diameter yielded no significant cutoff point for maximum sensitivity and specificity to predict the success of conservative treatment in AA (all $P > 0.35$). In the multivariate analysis, only the presence of ILF was found to predict conservative treatment failure (odds ratio = 10.2; 95% CI 3.3–31.8; $P = 0.001$), and hyperechoic fat was associated with a trend toward decreased need for surgery (odds ratio = 0.342; 95% CI = 0.114–1.026; $P = 0.056$).

The pathology results of children who failed conservative treatment showed 21 appendices with acute inflammation, 4 with subacute inflammation, and 1 without inflammation.

Discussion

This study evaluated the feasibility of conservative treatment for AA in children. We based indications for conservative treatment on our previous retrospective analysis [20], which showed that among 45 children with a diagnosis of uncomplicated AA, 40 (89%) were treated successfully with antibiotics alone. However, the previous study was underpowered to establish clinical practice, had a short follow-up of 3 months, and no pathology results after failed conservative treatment and surgery.

Therefore, in the current study, we prospectively analyzed 197 children with established AA who were eligible for conservative treatment with close, long-term follow-up. We showed that 87% of children with uncomplicated AA were managed successfully with conservative treatment that included IV antibiotic treatment for 3–5 days, oral antibiotics for 5 days, and long-term follow-up for a median of 18 months.

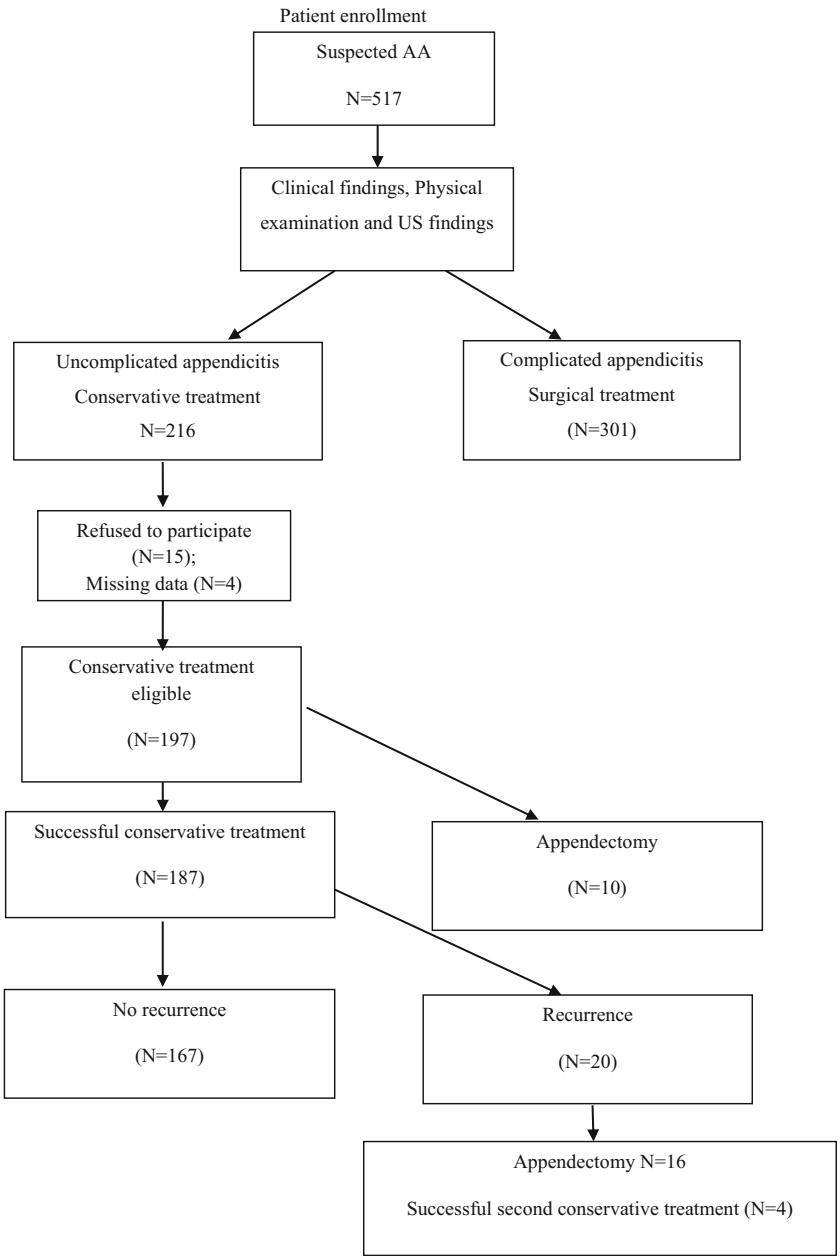

Fig. 1 Flow diagram of the diagnosis and management of children treated for acute appendicitis (AA)

Ten children failed conservative treatment and were operated within 4 days after admission, and another 16 children were operated with the diagnosis of recurrent AA within the follow-up period. Most operated children (96%) had pathology findings compatible with AA without perforation. The length of hospitalization in the operative group was longer than the conservative non-operative group while the length of antibiotic treatment was shorter. The reason for that might be because the operative group is a part of the initial non-operative group; therefore, if a child failed conservative treatment and underwent appendectomy, the child stayed longer in hospital; however, due to our pathological results indicating no gangrenous appendicitis, the antibiotic treatment was stopped earlier than the conservative treatment group.

Although non-operative treatment for uncomplicated appendicitis is now an accepted approach, there are few reports in children. Our 87% success rate in the current study was comparable to that in our previous pilot study and was in agreement with other reports showing success rates of more than 80% [12].

The current study evaluated two different diagnostic stages. The first was to distinguish between appendicitis and non-appendicitis abdominal pain. For this purpose, we used the Samuel scoring system[7] which includes clinical examination findings and laboratory values and is helpful in ruling out appendicitis. The second stage of diagnosis was aimed to differentiate between uncomplicated appendicitis where conservative treatment was

Table 1 Demographics of children who underwent initial conservative management for acute appendicitis

Variable	Successful conservative treatment ($N = 171$)	Surgery after failed conservative treatment ($N = 26$)	P value
Age (year)	10.2 ± 3.2	10.6 ± 3.0	0.49
Male sex, *n* (%)	112 (65.5%)	18 (69.2%)	0.83
Observation period after initial treatment (months)	18 (14–19)	16 (12–18)	0.56
Duration of pain before hospitalization (h)	19 (12–24)	22 (12–24)	0.30
Time from symptoms to management (h)	20 (12–28)	24 (15–28)	0.24
Temperature at admission (°C)	37.0 ± 0.6	36.9 ± 0.34	0.26
Nausea/vomiting, at admission *n* (%)	58 (33.9%)	15 (57.7%)	0.028[a]
Abdominal distention, at admission *n* (%)	3 (1.6%)	0	1.00
Diarrhea, at admission n (%)	22 (12.2%)	0	0.086
WBC at admission	12.3 ± 4.8	12.5 ± 3.8	0.86
Absolute neutrophils at admission	9.0 ± 4.4	9.8 ± 3.8	0.42
Lt shift (I/$T > 0.2$) at admission, *n* (%)	95 (52.7%)	11 (64.7%)	$P = 0.83$
CRP (mg%) at admission	0.57 [0.16–1.9]	0.78 [0.36–1.9]	$P = 0.44$
Hospitalization (h)	72 (60–84)	84 (72–126)	$P = 0.001$[a]
Duration of antibiotic treatment (IV and Oral) (days)	8.9 ± 1.24	8.2 ± 3.4	$P = 0.04$[a]

Data are presented as mean ± SD, number (%) or median (IQR)

WBC white blood cell, *IV* intravenous, *I/T* immature to total WBC ratio *CRP* C-reactive protein

[a] Significant difference compared to successful conservative treatment

indicated and preperforated appendicitis where immediate surgery was planned. Symptoms greater than 24 h before admission or diffuse tenderness, presence or suspicion of abscess or appendicolith on imaging, and significant comorbidities were considered contraindications for conservative treatment. Following this approach, only 13% of children with uncomplicated AA eventually needed surgery, with no perforated appendices among them. This indicates that our inclusion and exclusion criteria for conservative treatment were accurate.

Two disease markers were not part of the inclusion and exclusion criteria for conservative treatment: vomiting and ILF seen on the first US; both were more common in those who needed surgery. In the multi-regression analysis, only ILF was a significant predictive factor of failed conservative treatment. Therefore, we recommend adding the presence of ILF as a risk factor for conservative treatment failure. Whether presence of ILF should initiate surgery or a more prolonged antibiotic therapy deserves further evaluation. However, none of the failed conservative treatment AA with ILF had gangrenous changes. Our findings are in agreement with the study of Koike et al. [9] who showed that ILF was the only independent predictor of failed conservative treatment. Few studies looked at the difference between uncomplicated and complicated appendicitis in order to establish guidelines for conservative treatment in AA. In general, the findings presented in these studies were inconsistent. The results indicated different risk factors associated with perforation, including extremes of ages; male sex; delay in presentation or diagnosis; pain duration of more than 36 h; high WBC count and CRP level; and the presence of an appendicolith, extraluminal

Table 2 Ultrasound findings in the study groups (mean (SD) or *N* (%))

US findings	Conservative treatment ($n = 171$)	Surgery after failed conservative treatment ($N = 26$)	P value
External appendiceal diameter (mm)	7.76 ± 1.3	8.13 ± 2.1	$P = 0.23$
Hyperechoic fat	130 (72.2%)	11 (64.7%)	$P = 0.33$
Free fluid, *n* (%)	58 (32.2%)	7 (41.1%)	$P = 0.66$
Enlarged lymph nodes, *n* (%)	73 (40.5%)	10 (58.8%)	$P = 0.20$
Intraluminal appendiceal fluid, *n* (%)	42 (23.3%)	13 (76.5%)	$P = 0.037$*

* Significant difference compared to successful conservative treatment

US ultrasound

air, appendix diameter, free fluid, or periappendiceal inflammatory stranding on US or CT [2, 10, 13, 18]. Another study found no single factor that independently predicted perforation of appendicitis [3]. We did not find age to be a factor between successful and unsuccessful conservative treatment, although only seven children younger than 1 year were included in the cohort.

We selected only those children for conservative treatment whose duration of symptoms was less than 24 h. The hypothesis that a longer duration of complaints results in a greater risk of complicated AA is confirmed by other studies [5, 6, 15, 19]. One study showed that rupture risk was ≤2% in children with ≤36 h of untreated symptoms. For children with untreated symptoms beyond 36 h, the risk of rupture increased by 5% for each ensuing 12-h period [4].

The operative time and length of hospital stay for operative treatment at the time of recurrence after successful non-operative treatment were equivalent to those for operative treatment at the time of initial diagnosis in our study. This indicates that surgery after non-operative treatment for uncomplicated appendicitis was not more difficult. In our previous study [20], we observed four children with US findings of appendicolith at the time of initial non-operative management and all had early failure and operated with pathology revealed gangrenous changes. Therefore, we recommend that US detection of an appendicolith should be considered a sign of imminent perforation and surgery is indicated.

The most common organism causing appendicitis is *Escherichia coli*, followed by *Bacteroides* species, and then *Enterococcus*, *Streptococcus*, *Pseudomonas*, and *Klebsiella* species [14]. Therefore, we chose as our first-line antibiotic the third-generation cephalosporin ceftriaxone and metronidazole for *Bacteroides* species. Both antibiotics have a wide spectrum, covering both aerobic and anaerobic bacteria.

Appendectomy is a safe, well-established procedure with a good safety record, and when laparoscopy is used, it leaves little or no scarring [22]. However, few disadvantages are connected to appendectomy in uncomplicated AA. Appendectomy involves a general anesthesia (with its small but present risks) and the trauma and possible operative complications like bleeding, perforation, or adhesive bowel obstruction; furthermore, some suggest that the appendix is a well-suited reservoir for bacteria that normally constitutes the gut flor, and is needed to recolonize the bowel after bacterial infections, for example, diarrheal disease [16], On the other hand, conservative treatment was found to be cost-effective and was experienced more favorably by patients and parents [8], Our study could not address the issue of prolonged antibiotic treatment in the conservative management versus a shorter treatment in surgical approach; however, current studies are testing shorter duration of antibiotics in AA which may be tested even in the conservative treatment group [7]. For conservative treatment to be considered equivalent to appendectomy, some argue that the length of hospitalization should be similar [22]. In our large study, the length of stay was shorter for children in the conservative treatment group compared to children undergoing appendectomy. However, both were longer than recorded in other similar studies [1, 8]. A possible explanation for this is that we stipulated a minimum of 72 h of intravenous antibiotics in our conservative protocol, before the child could be discharged. In future studies examining this management, the time might be reduced.

The strengths of this study are its power to detect success in the conservative treatment, as well as its rigorous indications and contraindications for conservative treatment. The pathology findings of all those who were operated that showed AA with no perforations offer additional support to the management protocol.

This study has some limitations, the primary one of which is that it was a single-center study conducted at a hospital in which the physicians in charge of treating patients have radiology and pediatric surgery consultations available 24 h a day. It is possible that the prevalence of AA, the decision to perform complementary tests, and the availability of any of them (such as US) in a setting with different characteristics will make it necessary for our results to be applied as a function of these aspects. Second, the sample size and selection were subject to the presence of the investigators participating in the study and therefore may not accurately reflect the entire population of children with suspected AA. However, we believe that this does not significantly affect the results of the study where cases and controls were compared in a balanced manner. Another limitation is that, of the total of 197 patients, only 16 were younger than 6 years, representing only a small part of the sample. In this age group, in which the presentation tends to be more atypical, additional studies are needed to verify whether the performance of the described variables is similar to that found in older children.

In conclusion, this cohort study confirms the feasibility and safety of conservative treatment of early appendicitis in children. A rigorous diagnostic plan and indication with exclusion criteria were used, leading to few treatment failures without increased morbidity and with a low recurrence after 18 months of follow-up. Despite failures, offering a conservative approach to selected patients seems to reduce morbidity and enhances quality of life. The high incidence of AA in children more than justifies conducting this large-scale trial. Additional trials with different management policies or indications for conservative treatment are still warranted.

Authors' contributions Drs. Steiner and Arnon contributed to the study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision.

Drs. Buklan, Gutermacher, and Golani contributed to the study conception and design and to the acquisition of data.

Dr. Stackievicz contributed to the acquisition of data

Dr. Litmanovitz was involved in drafting the manuscript.

All authors approved the final version and agreed with its submission to the journal.

Compliance with ethical standards

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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 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Meir Medical Center, Kfar Saba, Israel. Informed consent was obtained from the parents of all individual participants included in the study.

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