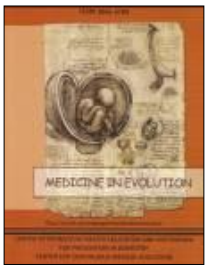
A SINGLE SITE, OPEN NON-CONTROLLED STUDY OF EFFICACY AND TOLERABILITY OF TWO FORMULATIONS OF THE MEDICAL DEVICE GENGIGEL ® BABY GEL (0.2% HYALURONIC ACID) IN THE TOPICAL TREATMENT OF TEETHING IN INFANTS



SERBAN ROSU[1], FABIO MONTANARO[2]

1. **Department of Oral and Maxillo-Facial Surgery, University of Medicine and Pharmacy "Victor Babeş" Timisoara, Romania,**
2. **Opera Contract Research Organization Genova, Italy**

ABSTRACT

The objective *of this study was to collect preliminary data on tolerability and efficacy on infants teething of two gel formulations of a high molecular weight Hyaluronic Acid (Gengigel® Baby), actually marketed as medical device. Main outcome parameters for efficacy were: pain, swelling, gingival rush, hyper-salivation, redness, abnormal teeth depth and mucosal laceration subcutaneous. In addition a comparison with previous Lidocaine administration and an Investigator assessment of overall therapeutic efficacy were performed.*

Conclusion: *These positive data will be the statistical bases to plan future clinical trial on Gengigel® Baby Gel.*

Key words: t*eething, hyaluronic Acid, clinical evaluation, topical treatment.*

Correspondence to:

Serban Rosu, MD, PhD
Adress: Str.Cozia 10, 300209 Timisoara (Romania)
Phone: +40 722313224
E-mail address: serbanrosu@yahoo.com

INTRODUCTION

The localized symptoms of teething vary between individuals [8]. Common symptoms as soreness and swelling of the gums before a tooth eruption are the cause for the pain and fussiness a baby experiences during this change. Teething can begin as early as 3 months and continue until a child's third birthday. Even if occasionally a slight rise of temperature may occur when the teeth come through the gum, generally teething has not been shown to cause fever or diarrhea [15]. A recent review on parents habits of relieving the symptoms associated with teething [12], evidenced the following: more than 50% of the 1500 participants allowed their infants to bite on chilled objects, 65.6% rubbed the gums with topical analgesics and 76.1% used systemic analgesics. Regarding the use of topical anesthetics present in a variety of prescription and non-prescription preparations for teething, it must be recorded that in 2003, there were 8576 exposures to local/topical anesthetics reported to the American Association of Poison Control Centers, with 67% of cases in the age group younger than 6 years old. According to the available literature involving topical anesthetic exposures in infants, from 1983 to 2003 there were 7 deaths in younger than 6 years old [4].

MATHERIAL AND METHODS

Study design: The study was a single-centre, pilot, open label, non-controlled trial planned as follows:

1st phase: 12 subjects treated with the 1st formulation of the tested drug;

2nd phase: 6 subjects treated with the 2nd formulation of the tested medical device; the trial was implemented in accordance with the Helsinki Declaration (and subsequent amendments) and performed following the Good Clinical Practice. All the patients enrolled gave their informed consent to taking part in the study.

Tested Medical Device: The Medical Device on study was a gel (0.2% HA) in 15 ml tube, already authorized as Medical Device(CE mark) of Class IIa as per Annex IX of the Council Directive 93/42/EEC.The two formulations of the Medical Device (named in the present article as 1st Gengigel® Baby gel and 2nd Gengigel® Baby gel, respectively) have the same Hyaluronic Acid (HA) concentration, but the 2nd Gengigel® Baby gel is more dense compared to the first formulation. The gel was administered three to five times a day by the parents applying it directly on the gingival tissue of the infant, massaging it on, with clean fingers.

Methods: Eighteen infants (aged between 6 and 36 months) suffering of teething were recruited. The infants were eligible if teething was diagnosed by the presence of at least 3 of the following clinical symptoms: pain, swelling, gingival rush, hyper-salivation, redness, abnormal teeth depth, subcutaneous mucosal laceration.

The exclusion criteria were: hospitalization and/or immobilization and/or confinement to bed; history of severe renal insufficiency, severe cardiac dysfunction or allergic reactions to HA and to any ingredient of the tested medical device.In addition were excluded the infants whose parents suffered from any form of psychiatric disorder or other condition

which, in the opinion of the Investigator, might invalidate the required prescription or complicate the communication with the subject. Within one day before the study and during the period of study was not permitted the concomitant use of Lidocaine or topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Concomitant treatment with Systemic NSAIDs was not allowed during the course of the study and within 3 day before.

The efficacy of the treatment was evaluated by Investigator at baseline, at day 3 visit and at final examination (after 7 days) on the basis of the following parameters:pain, swelling, gingival rush, hyper-salivation, redness. The parameters were arbitrarily scored according to intensity with the following VRS (Verbal Rating Scale): absent= 0, moderate= 1, intense= 2.

The following additional secondary efficacy parameters were assessed by Investigator at day 0, 3 and 7 of treatment: abnormal teeth depth (scored according to intensity with the following VRS minimal= 0, moderate= 1; extreme= 2) and mucosal laceration subcutaneous (scored as: minimal= 0, perceptible= 1; intense= 2). During the study period the parents were instructed by Investigator to collect on diary cards and daily assessed the day pain, night pain, swelling, gingival rush, hyper-salivation. These parameters were scored for intensity according to the following VRS: absent=0, moderate=1, intense= 2. For a global rating of the comparison with previous Lidocaine administration was used the following VRS: 1 = no difference; 2 = minimal difference; 3 = moderate difference; 4 = intense difference; 5 = very intense difference. At the end of the study, the Investigator expressed an assessment of the overall therapeutic efficacy: very good: symptom-free (complete symptom remission); good: considerably improved; satisfactory: moderately improved; poor: unchanged (persistence of symptom score); very poor: worsening (progression of symptoms).

As far as tolerability of the study treatment was concerned, the occurrence of adverse events during the trial was monitored. The overall assessment of tolerability *by the Investigator* was expressed at the final examination by means of the following score: very good (no adverse events, nor organic toxic diseases and good acceptability of the treatment by infant); good (no adverse events and organic toxic diseases); moderate (slight and transient adverse events); poor (persistent adverse events); very poor (severe adverse events and organic toxic diseases).

Statistical analysis: Statistical analysis were performed using the SAS statistical package version 9.2 (SAS Institute Inc, US). The data concerning all the variables were presented by means of usual descriptive statistics: mean standard deviation (SD), standard error of the mean (SE), median, minimum and maximum, absolute and relative frequencies.

Two-tailed tests were used for the parameters analysed and a 5% level of statistical significance was chosen. The non-parametric data were analysed by means of the Wilcoxon tests.

RESULTS

Pain: Pain reduction between the two time-points (baseline and day 7) was statistically significant ($p<0.01$) within the whole population of 18

treated subjects (fig. 1); also considering separately the group of infants treated with the 1st formulation of Gengigel® Baby gel and the group treated with the 2nd formulation of Gengigel® Baby gel, a statistically significant difference ($p<0.01$) was evidenced in the mean pain reduction.

Swelling: In the 18 infants, the values of the swelling intensity, evaluated by a 3 points VRS, were absent = 0, moderate = 7 and intense = 11 at baseline, while after 7 days of treatment (final visit) were changed as follows: absent = 6, moderate = 12 and intense = 0. The difference between the values at the time of the final examination and at baseline ($p<0.01$) was statistically significant (fig. 2). In addition, the reduction from baseline to the final examination was statistically significant ($p<0.01$) also in the group of 12 infants treated with the 1st formulation of Gengigel® Baby gel.

Gingival rush: The decrease of this parameter between the two -points (baseline and day 7) was statistically significant within all population treated (18 subjects, $p<0.01$) (fig. 3); on the other hand the same statistical significance ($p<0.01$) was evidenced within subjects treated with the 1st formulation of Gengigel® Baby gel group.

Redness: At the final examination, the total population and both the study groups treated (12 and 6 infants, respectively) showed a statistically significant decrease of the symptom redness (fig. 4).

Hyper-salivation: Good improvement of this symptom ($p<0.01$) occurred in the global population treated (at baseline: absent = 0, moderate = 4 and intense = 14; at the final visit: absent = 0, moderate = 17 and intense = 1; (fig. 5) and it had decreased significantly ($p<0.01$) also within the group of 12 infants treated with the 1st formulation of Gengigel® Baby gel.

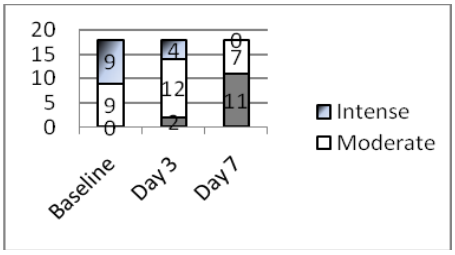


Fig.1 Pain reduction between the time-points within the whole population of 18 treated infants ($p<0.01$ between baseline and day 7).

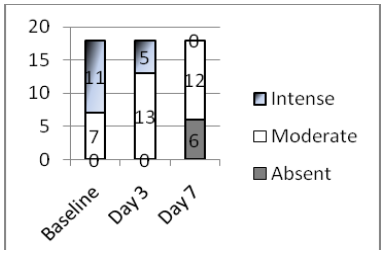


Fig.2 Swelling between the time-points within the whole population of 18 treated infants ($p<0.01$ between baseline and day 7).

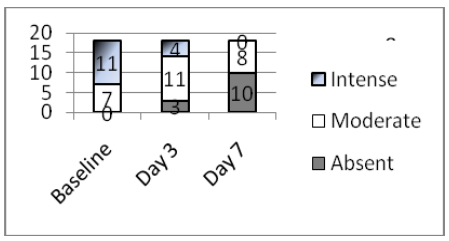


Fig.3 Gingival rush between the time-points within the whole population of 18 treated infants ($p<0.01$ between baseline and day 7).

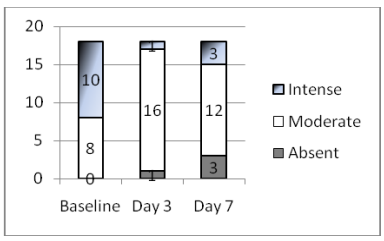


Fig.4 Redness between the time-points within the whole population of 18 treated infants ($p<0.01$ between baseline and day 7).

Teeth depth, mucosal laceration: No statistically significant difference was evidenced for the parameters abnormal teeth depth and subcutaneous mucosal laceration, nor in the total population (18 infants), nor in the two groups treated with the 1stGengigel® Baby gel or the 2ndGengigel® Baby gel formulation.

Investigator's global assessment: The overall assessment was very satisfactory with reference to the total infants treated (Table 1) In fact the assessment confirmed the above mentioned results: good or very good efficacy (67.67%), satisfactory or good duration of effect (83.33%) and rapidity of effect (72.22%). The results performed by the two different Gengigel® Baby gel formulations can be considered superimposable. Anyway, these positive results should be considered carefully as the number of subjects analyzed is quite low.

Table 1 Investigator's Global Overall Assessment at the end of treatment period (18 subj).

	Very poor	Poor	Satisfactory	Good	Very good
Efficacy	0 (0%)	2 (11,2%)	4 (22,2%)	11 (61,1%)	1 (5,5%)
ration of effect	0 (0%)	3 (16,6%)	7 (38,8%)	7 (38,8%)	1 (5,5%)
apidity of effect	0 (0%)	5 (27,7%)	9 (50%)	3 (16,6%)	1 (5,5%)

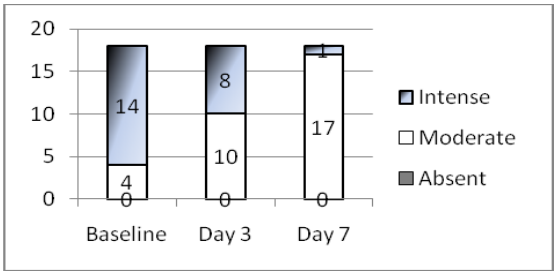


Fig.5 Hyper –salivation between the time-points within the whole population of 18 treated infants ($p<0.01$ between baseline and day 7).

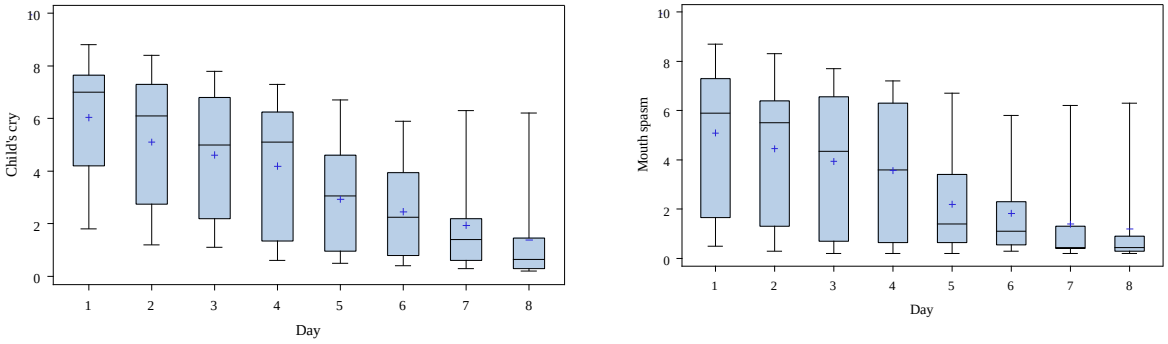


Fig.6 Boxplots of the evaluation of infant cry (a) and mouth spasm (b), using VAS scores, by day as reported on diary cards; infants treated with 1st formulation of Gengigel® Baby gel (12 subjects).

\+ = mean values

Investigator's comparison with previous Lidocaine use: For this 5-point-VRS scores observed at the final visit for treated infants the Investigator appreciated a minimal or moderate difference in 50% and an intense difference in 50% of subjects treated with the 1stGengigel® Baby gel, while

the comparison between the 2nd Gengigel® Baby gel formulation and the previous Lidocaine use evidenced a minimal or moderate difference in 83.34% and an intense difference in 16.67% of treated cases.

Other symptoms: Additional considerations can be made on the twelve subjects treated with the 1st Gengigel® Baby gel formulation, as diary cards were collected by parents. In these the infants cry (fig. 6) and mouth spasm analysis reduction (VAS mm) confirmed the positive results for Gengigel® Baby gel formulation, as previously evidenced. In addition a general trend to improvement was evidenced with score 0 since day 3 and 4 for daily pain, night pain and gingival rush.

Tolerability and Adverse Events: Tolerability was good in all the treated infants. The only adverse events were reported with the 1st Gengigel® Baby gel formulation administration: fever and diarrhea. Both were considered moderate and not related with the study medication. No serious adverse event or reaction was reported during the study. In addition the Investigators' global safety assessment confirmed the safety and tolerability of the study medications. All these observations are supportive of an excellent tolerability profile.

CONCLUSION

The rapid change in the oral cavity during paediatric age requires fast renewal of periodontal tissues. HA, a polysaccharide naturally occurring inthe oral mucosa, plays an essential role in maintaining the functional balance required for intercellular exchange. In fact, depletion of HA results in a consequent reduction of the protection mediated by the oral mucosa. Several pre-clinical and clinical studies [1, 2, 4, 6, 16, 11] highlighted the anti-inflammatory, regenerating, healing action and anti-edematous function of HA in the treatment of pathological conditions of oral cavity. Recently, several products containing high molecular weight HA have been developed; In particular, since 2000, Gengigel® Baby, the gel formulation tested in this trial, has been marketed in various European countries for gingival inflammatory conditions or gums trauma, as well as for any condition where the gingival mucosa requires increased concentrations of HA. This medical devices characterized by the absence of preservatives, alcohol and dyes; therefore its administration in children, and particularly in infants is safe and can help creating a natural protective layer on the gingival tissue. In previous clinical trials [5, 7, 9, 10, 13, 14] Gengigel® Baby gel was able protect the mucosa, by preventing the deficiency of natural gingival HA. The result is a periodontal tissue/fluid balance with accelerated healing and repair properties. These properties could be of interest either for accelerating the wound healing process, or for treating the complex physical symptoms (i.e. soreness and swelling of gums, crying, sleeplessness, restless sleep at night and mild fever) related to teething in infants. Gengigel® Baby was considered particularly suitable for this clinical trial based on the direct knowledge derived from the clinical practice, and on the absence of any contraindications (other than hypersensitivity to HA and excipients), precautions or warning. In addition it must be noted that no Adverse Drug Reaction (ADR) were reported during the 10 years marketing timein Europe. In this open, non-

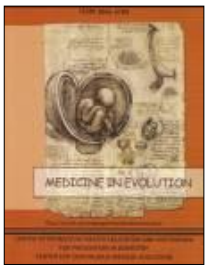
controlled study the two tested gel formulations had the same HA concentration and different density and were administered three to five times a day by the parents. The aim of the study was not to identify a difference in the efficacy of the two formulations, but to collect preliminary data on the outcome tested in order to plan future clinical trials. In this respect all infants enrolled in this trial, irrespective of the formulation used, showed an improvement of the symptoms: in fact the 18 treated subjects there was a statistically significant ($p \leq 0.01$) difference between day 0 and day 7 for the primary variables of interest (i.e. pain, swelling, gingival rush, hyper-salivation, redness). The study showed that this positive evaluation of Gengigel® Baby is reported not only by the Investigator (through the assessment of symptoms at different visits and by the global assessment reported at the final visit), but also by the parents in the diary cards.

The tolerability of both formulations is supportive of an excellent tolerability profile: only two moderate adverse events, unrelated to the study gel were reported (fever and diarrhoea). This study confirms the previous clinical experiences, showing that Gengigel® Baby can be considered a useful therapeutic tool for the treatment of teething in infants: these positive data will be the statistical bases to plan future clinical trials.

REFERENCES

1. Bartold, P.M. Platelet-driven growth factor stimulates hyaluronate but not proteoglycan synthesis by human gingival fibroblasts in vitro. J Dent Res 1993, 72: 1473-1480.
2. Bartold, P.M. The effect of interleukin-1-beta on Hyaluronic acid synthesized by adult human gingival fibroblasts in vitro. J Periodontal Res 1988, 23: 139-147.
3. Curtis LA, et al., Are one or two dangerous? Lidocaine and topical anesthetic exposures in infants.J Emerg Med. 2009 Jul; 37(1):32-9. Epub 2008 Feb 14. Review
4. Irwin, C.R., et al., Effects of cytokines on gingival fibroblasts in vitro is modulated by the extracellular matrix. J Periodontal Res 1994, 29: 309-317
5. Jervoe-Storm, X. et al., Employ of locally applied hyaluronic acid during a three mont initial treatment. Paradontologie. 2003; 14/1:41-49
6. Kim SK et al., The effect of hyaluronic acid on anti-inflammatory action in mouse. J Korean Assoc Oral Maxillofac Surg. 2010 Feb;36(1):16-22
7. Mantovani S et al., Preliminary clinical evaluation of a hyaluronic acid based product in oral disorders: double blind trial AttualitàTerapeuticaInternazionale. 1998; 7: 1-3.
8. McIntyre GT, McIntyre GM. Teething troubles? Br Dent J. 2002 Mar 9;192(5):251-5
9. Mesa FL et al., Antiproliferative effect of topic hyaluronic acid gel. Study in gingival biopsies of patients with periodontal disease. Histol Histopathol.2002; 17(3):747-53. PubMed PMID: 12168783.
10. Nobre de Araújo M et al., Peri-implant maintenance of immediate function implants: a r randomized controlled clinical trial comparing hyaluronic acid and chlorhexidine. Int J Dent Hyg 2007; 5:87-94.
11. Oksala, O. et al., R. Expression of Proteoglycans and hyaluronan during wound healing. J HistochemCytochem 1995, 43: 125-135.
12. Owais AI et al., O. Challenging parents' myths regarding their infants's teething.Int J Dent Hyg. 2010 Feb; 8(1):28-34.
13. Pagnacco A., et al., Double blind clinical trial vs. placebo of a new sodium hyaluronate-based gingival gel. Attualità Terapeutica Internazionale. 1997; 4: 1-7.
14. Pistorius A et al., The clinical application of hyaluronic acid in gingivitis therapy.Quintessence Int. 2005 Jul-Aug; 36 (7-8):531-8.
15. Tintinalli, Judith (2004). Emergency Medicine: A Comprehensive Study Guide, Sixth edition. McGraw-Hill Professional. p. 1483
16. Weigel, P.H. et al., A model for the role of Hyaluronic acid and fibrin in the early events during inflammatory response and wound healing. J. TheorBiol 1986, 119: 219-234.

COMPARATIVE STUDY OF EDUCATIONAL ORAL HEALTH PROGRAMMES ON THE WORLD



ZEICU CORNEL[1], PODARIU ANGELA CODRUTA[2], POPOVICI RAMONA AMINA[2], SAVA-ROSIANU RUXANDRA[2], JUMANCA DANIELA[2], OANCEA ROXANA[2], GALUSCAN ATENA[2]

1. **PHD student at University of Medicine and Pharmacy "Victor Babes", Timisoara;**
2. **Department of Preventive Oral Health, Faculty of Dentistry, University of Medicine and Pharmacy "Victor Babes", Timisoara**

ABSTRACT

Health promotion is the process of enabling people to increase control over, and to improve, their health. Children with caries have a slower growth rate compared with children without it, which can be attributed to the pain during eating. Oral health promotion focuses largely on disease, and health is defined as the absence of caries and periodontitis. Oral health education aims to impart knowledge to people and influence their choice of lifestyle. Oral health education for children should be considered a priority. School instructors play an important role in achieving the best oral health outcomes for school children because in some areas children have limited access to dental care and the school instructors are the first health professionals to come in contact with children. The prevalence of childhood caries is a public health problem. According to statistics, 61% of 6-12-year-old children have at least one tooth cavity, and/or filling in their deciduous teeth, and 40% of 6-14-year old individuals have at least one cavity and/or filling in their permanent teeth. Traumatized baby teeth may lead to tooth loss and, among other factors such as childhood illnesses, may affect the developing permanent teeth. It is therefore important to prevent dental trauma in children. A safe environment at home, in schools and in the community, including safer playgrounds and roads with well-organized traffic, can help minimize the risks.

Key words: *Oral Health, Educational Programmes, Impact, children, school education*

Correspondence to:

Popovici Ramona Amina
Adress: UMF "Victor Babes" Timisoara, Faculty of Dentistry, Department nr. 1,
Splaiul Tudor Vladimirescu nr. 14A
Phnone: 004-0722 401 383
E-mail address: ramonaamina@yahoo.com