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► To cite this version:

Guillaume Doucède, Annie Morch, B. Pouseele, P. Lecomte-Grosbras, M. Brieu, et al.. Evolution of the mechanical properties of a medical device regarding implantation time. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 2019, 242, pp.139-143. 10.1016/j.ejogrb.2019.08.021 . hal-02942189

HAL Id: hal-02942189

<https://hal.science/hal-02942189v1>

Submitted on 20 Jul 2022

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Evolution of the mechanical properties of a medical device regarding implantation time

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31 **Abstract**

32 *Background.* Our study aimed at understanding the influence of healing time on the
33 mechanical properties of meshes used in pelvic organ prolapse, once implanted in an
34 animal model using the rat.

35 *Methods.* A standard polypropylene mesh was implanted in 42 rats in order to
36 evaluate the mechanical properties of the implanted mesh. Explantation occurred at
37 1, 2, 3, 4 and 5 months and mechanical tests were performed. Each sample was
38 mechanically evaluated by a uniaxial tensile test with a machine (BIOTENS).
39 Biological tissues presented a nonlinear relation between stress and strain so it could
40 be modeled by the 2 parameters C_0 and C_1 of a second-order Mooney-Rivlin law.

41 *Results.* The rigidity in small deformation might not be affected by healing time or the
42 presence of the synthetic implant. On the contrary, changes seemed to occur on the
43 stiffness in large deformation (C_1). The stiffness with the mesh composite changed
44 with healing time. The “two-month implantation” rat group was significantly more rigid
45 than the two control groups ($p_{\text{control}/2\text{months}}=0,04$ and $p_{\text{placebo}/2\text{months}}=0,04$). The 2- and 3-
46 month healing groups were significantly more rigid than the 1-month healing group
47 ($p^{1/2\text{months}}=0,01$ and $p^{1/3\text{months}}=0,003$). After 2 months, the mechanical properties
48 seemed to stabilize ($p^{2/3\text{months}}=0,44$, $p^{2/5\text{months}}=0,16$ et $p^{3/5\text{months}}=0,3$).

49 *Conclusion.* In order to evaluate the mechanical properties of an implanted mesh, the
50 optimal time for explantation seems to be 2 months. Once this period is over, a more
51 physiological mesh will be developed in order to be similar to native vaginal tissue
52 once implanted and colonized by scar tissue.

53

54 **Key Words:** *genital prolapse, mesh, biomechanical properties, transvaginal repair,*
55 *healing time*

56 **Introduction**

57

58 Success of surgical meshes in general surgery, combined with the high failure
59 rates of traditional native tissue repair, has led gynecologic reconstructive surgeons
60 to use mesh materials [1]. The use of synthetic meshes for the treatment of prolapse
61 started in the 1990s. As the feasibility was confirmed by some early studies [2], the
62 use of these synthetic meshes became quickly popular [3]. The use of prostheses
63 brings about specific complications that are not without any consequences [4].
64 Because of these complications, several warnings from the Food and Drug
65 Administration proved to be necessary [5]. We think that these complications are
66 caused by unsuitability between the mechanical properties of the **prolapse** mesh and
67 mechanical properties of the vaginal tissue because the first synthetic meshes were
68 used for hernia repair [6]. The abdominal wall role is crucial: it protects and maintains
69 the abdominal cavity. On the contrary, genital organs have a physiological large
70 mobility, which is essential for the rectal, urinary and sexual functions [7]. A mismatch
71 between the mechanical characteristics of the mesh and the pelvic tissue seems to
72 contribute to the occurrence of specific complications with meshes [4]. Before
73 commercialization, **IUGA change to recommended the undertaking of** in-vivo tests
74 since meshes are still mostly evaluated ex-vivo, *i.e.* in a "dry" condition (in opposition
75 with explanted meshes) [8]. Indeed, studies of dry meshes currently neglect the
76 evolution of the mechanical properties of implanted mesh related to scar tissues after
77 implantation. When the mesh is implanted, it forms a composite with scar tissue. The
78 mesh should be designed according to the mechanical properties of the targeted,

79 non-pathologic, tissues. Our study aimed at offering a new experimental protocol on
80 rat model, studying the influence of healing time on the mechanical properties of the
81 explants, in order to determine the necessary time for the explants (prosthesis and
82 scar tissue) to have stable mechanical properties.

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86 **Materials and methods**

87 **1. Experimental animals**

88 A total of 42 male Wistar rats were used in this study, which obtained ethics
89 committee approval n° 3061. Animals were housed with a 12-h alternating light–dark
90 cycle and provided free access to food and water. Seven groups of six rats were
91 composed. Five groups were implanted with meshes and we created two other
92 groups: a control group (6 rats) that received no surgery and a placebo group (6 rats)
93 that received a surgery (dissection of the abdominal fascia but without implantation
94 meshes). Mechanical tests were performed on raw mesh, before implantations
95 started.

96 **2. Mechanical tests**

97 **2.1 Prosthesis**

98 For this study we used a Type I polypropylene monofilament prosthesis,
99 measuring 80µm in diameter (Amid Classification). This polypropylene monofilament
100 mesh was macroporous because this remains the “gold standard” for pelvic prolapse

101 mesh. The prosthesis we chose to implant had previously been the subject of a pre-
102 clinical study and its choice was discussed between doctors from the *CHRU of Lille*,
103 mechanical engineers, and textile manufacturers. No information on mechanical
104 properties of the prosthesis can be disclosed for reasons of data confidentiality.
105 Mechanical testing was performed on each collected specimen. The influence of
106 healing time was studied: explants were taken off at **zero, one, two, three, four and**
107 **five** months of healing. “Control group” rats were sacrificed from the beginning of our
108 study on **M0 (month zero)**. Drawing on a study by Röhrnbauer and Mazza [9], we
109 **modelled** the explanted composite by a composite made of elastomer and our textile.
110 The sample size was decreased from 20cm long and 5cm wide (standard testing
111 dimension of a textile) to 3cm long and 2cm wide without any mechanical differences.
112 Beyond those dimensions, the size of the sample is no longer representative (picture
113 1). For that reason, we implanted 7-cm long and 5-cm wide prostheses, which took
114 into account the above data.

115 **2.2 Mechanical tests**

116 Each sample was mechanically evaluated by a uniaxial tensile test with a machine
117 (BIOTENS). We designed for biological tissue testing provided with a 100 N load cell.
118 Displacement rate was set at 5mm/min. The stress and strain were computed. Stress
119 is the force per section unit: $\sigma = F/S_0$, with F effort in Newton (N) and S_0 the initial
120 cross-section in mm^2 . Strain is computed with the measure of displacement:
121 $\lambda = 1 + (L/L_0)$, L is the current displacement and L_0 the initial length between the grips.
122 Biological tissues presented a non-linear relation between stress and strain (Fig. 1).
123 Previous studies [9] showed that it can be **modelled** by the 2 parameters C_0 and C_1 of
124 a second-order Mooney-Rivlin law. C_0 represents the rigidity in small deformation and

125 C₁ the rigidity in large deformations. This study protocol has been used and approved
126 on ewe tissues and on connective human tissue [10].

127 **3 Surgical Technique**

128 **3.1 Implantation**

129 After the rat was asleep, its abdomen was shaved. An injection with
130 buprenorphine was given for local pain treatment. A median vertical abdominal
131 cutaneous incision of 5cm was performed. The abdominal fascia was then dissected
132 sufficiently to place the mesh. The mesh was fixed to the abdominal fascia and
133 muscles in the 4 corners with a single suture of a non-absorbable monofilament
134 **suture** (Prolene 2/0, Ethicon, Johnson & Johnson®). The skin was sutured using
135 single points of an absorbable **suture** (Polysorb 2-0, Covidien®).

136 **3.2 Explantation**

137 After induction box, the rat was sacrificed using a 2mL lethal intracardiac
138 injection of T61. The median incision was re-performed, and a dissection of the
139 mesh-tissue complex was performed. After total liberation of the mesh from the skin
140 tissue, a full-thickness resection of the abdominal wall (mesh + fascia + muscle +
141 peritoneum) was performed. Thereafter, the re-sected tissue was immediately placed
142 in physiologic water for transport to the place where the mechanical testing was
143 performed.

144 **4 Statistical analysis**

145 The data from the explanted mesh-tissue composite were compared. A Kruskal-
146 Wallis test followed by a post-hoc Mann-Whitney U-test was performed with R. A p-
147 value less than 0.05 was considered significant.

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154 **Results**

155 We observed four deaths in our study (9,52%) and mesh exposure concerned
156 5/28 (17,85%) rats and we were not able to get information on the two deceased rats
157 because the animal facility got rid of them before we could observe their abdominal
158 wall (Table 1).

159 The abdominal wall was tested for each group with meshes. However, we were at
160 least able to test four samples in each group, except for the group with implantation
161 at four months in which we could only test two samples. The reason was **that** it made
162 it impossible to extract mechanical data from **the prosthesis as is it was either too**
163 **retracted or too exposed**, or even because of the death of the animal. So, we could
164 not present the four months implantation results because of the small number of
165 animals in this group (two rats).

166 The results of the mechanical tests are summarized in Table 2.

167 Firstly, we did not find significant differences in the C_0 coefficients at 1, 2, 3, 5
168 months in control or placebo groups. The rigidity in small deformation might not be

169 affected by healing time or the presence of the synthetic implant. **On the contrary, the**
170 **stiffness in large deformation (C_1) is affected by healing time.** The influence of
171 healing tissue was studied in 2 control groups. There was no significant difference
172 between control and placebo groups for C_0 and C_1 coefficient ($p_{\text{control/placebo}} = 0.93$ and
173 $p_{\text{control/placebo}}=0.58$). Then we noted $p^{i/j\text{months}}$ the p-value comparing the group months
174 of healing to the j months group. The 2- and 3-months healing groups were
175 significantly more rigid than the 1-month healing group ($p^{1/2\text{months}}=0,01$ and
176 $p^{1/3\text{months}}=0.003$). After 2 months, the mechanical properties seemed to stabilize
177 ($p^{2/3\text{months}}=0.44$, $p^{2/5\text{months}}=0.16$ et $p^{3/5\text{months}}=0.3$) (Fig 2).

178 **Discussion**

179 Our study provides considerable information on a minimum implantation period of
180 2 months before being able to determine the mechanical properties.

181 **1. Animal models**

182 Several animal models can be used for the study of genital prolapse: rats, mice,
183 pig, rabbits, sheep and nonhuman primates. The aim of our study was to investigate
184 the mechanical **behaviour** in-vivo of the prosthesis made of scar tissue. We were
185 able to demonstrate that it was necessary to work with a minimal prosthesis size of
186 3x2cm in order to obtain significant mechanical data [11]. Hence, it was not
187 appropriate to use pig, ewe or non-human primates. Rat, mice or rabbit were the
188 possibilities left to us. The rat is an animal model that presents several advantages,
189 on the economical (low cost of purchase) and practical (small, storage, maintenance
190 and sacrifice) levels as well as from and from the point of view of durability [12]. We
191 therefore chose the rat for all the reasons above-mentioned but also because it is a
192 widely used animal model for the understanding of genital prolapse [13].

193 **2. Healing time**

194 Healing process is a phenomenon that occurs over several weeks and that
195 intercedes with various factors. Indeed, after the “acute” phase, there comes a
196 chronic phase in which the definitive scar tissue appears. These different phases
197 involve crucial components for the formation of a definitive scar tissue in response to
198 a foreign material [14-15]. We think it is essential, in a research protocol for the
199 design of a new prosthetic material, to take account of the healing process, and
200 therefore the in-vivo evolution of the prosthesis, to retrieve the mechanical properties.
201 The study on the animal model appears therefore an essential step before the
202 commercialization of new prosthetic implants, in order to prevent withdrawal of some
203 devices by laboratories after successive recalls from the Food and Drug
204 Administration [8]. This is all the more important because the prosthesis used in
205 genital prolapse corrective surgeries are nowadays the subject of extreme lobbying
206 that can sometimes lead to undermine the use of these materials in some cases.

207 The comparison of our data with data from the literature is difficult for several
208 reasons. On the one hand, there is a large heterogeneity among animal models
209 used. It is therefore more difficult to provide relevant results when we compare
210 mechanical properties between two different animal models. Currently, there is no
211 comparative data on the mechanism (cellular, histological, immunohistochemical)
212 involved in the healing process between the various animal models used.

213 On the other hand, our study relies on a biomechanical law (Mooney-Rivling
214 Law), which is not used by the other teams in this particular field. Previous studies
215 published in literature on human pelvic tissues have highlighted that pelvic tissues
216 (bladder, rectum, vagina, ligament) could behave according to that law. Hence, our

217 study was based on this law and the comparison between coefficient C_0 and C_1 . In
218 light of these elements, it is therefore more difficult and less relevant to compare our
219 data to the one used by the other teams.

220 To our knowledge, there is only few data in the literature on the impact of healing
221 time on mechanical properties of a mesh in pelvic organ prolapse on rats or on other
222 animal models. Our study is an important source of information because it is
223 necessary to wait a minimum of two months before extracting prosthetic explants in
224 order to study their mechanical properties. There is no comparable study to ours in
225 this area; however, we could find in the literature some studies focusing on explants
226 rigidity at various implantation times, without specific mentions of the healing
227 process.

228 Hernandez Gascon et al. [16] with rabbit model demonstrated that prosthesis
229 rigidity was more important after 180 days of implantation compared to 3 months and
230 2 weeks of implantation without observing any statistically significant differences
231 between 3 and 6 months. Nevertheless, the rigidity of the meshes was still evolving
232 after 6 months. Melman et al. [17], on pig, did not observe any statistically significant
233 differences concerning rigidity after implantation of two meshes for 1, 3 and 5
234 months. In Ulrich et al. [18], explant rigidity was not the same according to the
235 various times of implantation, with a more important rigidity at 3 months than at one
236 week, and a bi-linear curve at 3 months that is corroborated in our study. This data
237 was also highlighted in Konstantinovic et al. [19] who studied the evolution of
238 mechanical properties of prostheses at 1 week, 2 weeks, one month and 4 months.
239 Finally, O Sullivan et al. [20] also determined a 3 months integration period of the
240 prosthesis in the abdominal wall of the rat. To ensure that 2 months are required, we

241 extended the healing durations up to 5 months. We think that our animal model,
242 which is different from other animal models, can explain our results.

243 The overall of the studies highlights that explant rigidity increases with time,
244 without showing any statistically significant differences. Our study therefore brings
245 complementary information on the study of mechanical properties of explants in the
246 rat. Hence, in regard of the overall results, we can estimate that it is necessary to
247 wait a minimum of two months before extracting prosthesis to study its mechanical
248 properties.

249 **3. Complications**

250 Regarding the rate of exposure of the prostheses on the animal model, it is
251 estimated of 16.66% in our study. We have very little literature data on the rate of
252 exposure for rats. This element is not mentioned in most of studies using the rat as
253 an animal model. This can be due to a too short implantation time (less than 3
254 months) in the various research protocols [21-23]. Regarding other models, we notice
255 very heterogeneous rates of exposure between 10%-30% for De Tairac et al.,
256 Manodoro et al. or Endo et al. [24-25]. This heterogeneous rate of exposure certainly
257 depends on the type of prosthesis implanted, the implementation location and finally
258 the animal model used. We can see that we have, with this animal model, a fairly
259 satisfactory rate of exposure with respect to the rates reported in the literature;
260 however this rate of exposure shall be carefully interpreted because it would need to
261 be realized individually, in every implantation group, in order to determine a
262 significant difference.

263 There are two main shortcomings in our study. On the one hand, the small
264 number of animals within the groups can limit the interpretation of our results. We

265 were limited in the number of animals for this preliminary study because the project
266 contains three other trial groups with a limited number of animals that we had to
267 respect for ethical reasons. On the other hand, we did not make any histological
268 descriptive study to explain this increase and then stabilization of the- rigidity of
269 implants. We cannot establish any reason for the gradual increase. It was already the
270 case in other studies.

271

272

273 **Conclusion**

274 A minimum period of two months seems necessary in order to retrieve the
275 mechanical properties for the design of prosthetic devices. This period takes account
276 of the healing process, resulting in the integration by the host of this foreign material.
277 The data we provide in this article corroborate those from the literature regarding
278 minimum time of implantation 2 to 3 months that is necessary for mechanical
279 properties of prostheses to stabilize. Such minimum time of implantation to be fulfilled
280 before any study of the mechanical properties of prostheses essential because it
281 would undoubtedly make it possible to design more physiological medical devices
282 (taking into account the process of healing particular and thus reduce the risks of
283 complications related to these prostheses.

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288 **Acknowledgements:** ANR (National Agency Research): ANR-13-TEC-0003-01
289 and we are grateful to DHURE (Département Hospitalo-Universitaire de Recherche
290 Expérimentale, Université Lille2) for their assistance.

291

292 **Conflict of interest**

293 Michel Cossson: Disclosures for teaching sessions, expert meetings and round table
294 : FRESENIUS, ALLERGAN, BOSTON SCIENTIFIC.

295 Guillaume Doucède, Annie Morch, Pauline Lecomte-Grosbras, Mathias Brieu and
296 Chrystèle Rubod : None

297

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Figure 1: Illustration of the bilinear behaviour of a biological tissue (example shown with a sample of rat abdominal wall)

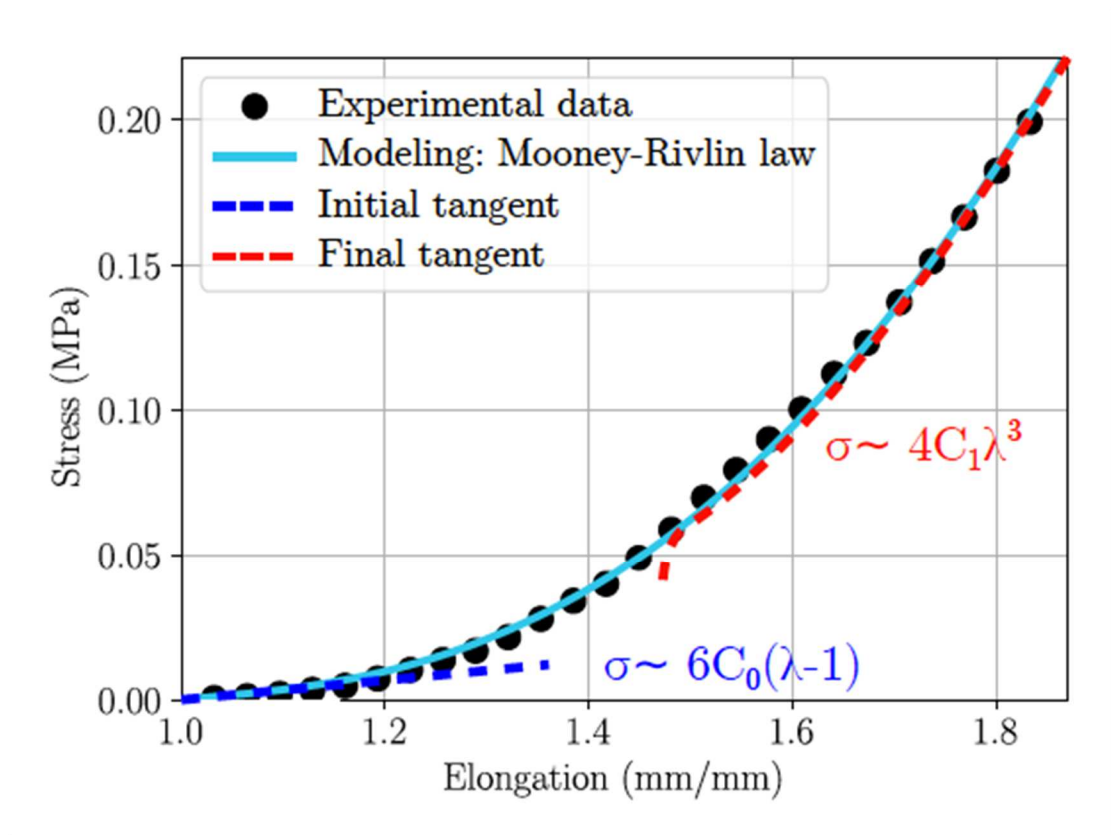


Fig 2: Representation of the median rigidity (interquartile range) in small (C_0) and large deformation (C_1) for control groups and different healing time (4, 8, 12, 20 weeks). Temoin = Control

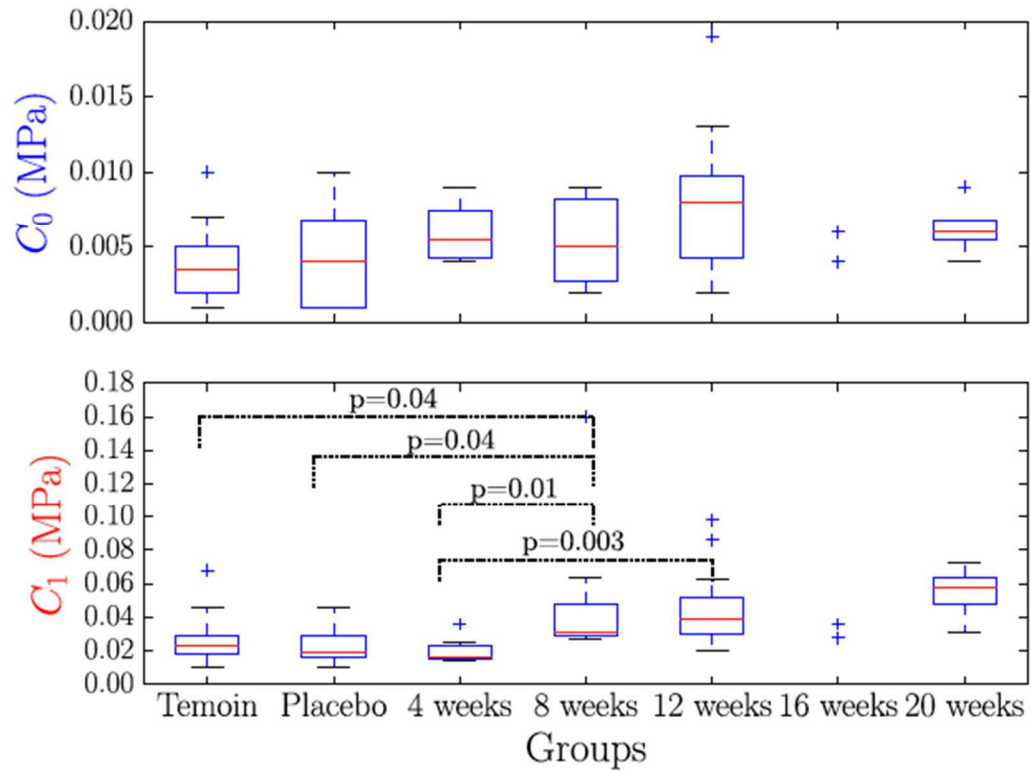


Table 1: Clinical complications

Explantation time	Number of rats	Clinical complications :		
		Mesh exposition	Death	Shrinkage
1 month	6	1	0	1
2 months	6	0	0	2
3 months	6	1	0	1
4 months	6	3	1	0
5 months	6	0	1	1
Control Group	6	0	1	0
Placebo	6	0	1	0
Total	42	5/28	4/42	5/28
Results (%)		17,85%	9,52%	17,85%

Table 2: Evolution of C_0 and C_1 according to the time of implantation.

	C0 (MPa)						95 % CI
	Median	Q1	Q3	Q3-Q1	mean	SD	
One month	0,006	0,004	0,008	0,004	0,004	0,002	0,003200667
Two months	0,005	0,003	0,008	0,005	0,005	0,003	0,004157788
Three months	0,008	0,004	0,01	0,006	0,007	0,004	0,003695811
Four months	0,005	0,004	0,006	0,002	0,005	0,001	0,001600333
Five months	0,006	0,006	0,007	0,001	0,006	0,002	0,00392
Control	0,004	0,002	0,005	0,003	0,004	0,002	0,002095328
Placebo	0,004	0,001	0,007	0,006	0,005	0,003	0,00339482

	C1 (MPa)						95 % CI
	Median	Q1	Q3	Q3-Q1	mean	SD	
One month	0,016	0,015	0,023	0,008	0,02	0,008	0,012802666
Two months	0,032	0,029	0,037	0,008	0,036	0,012	0,016631151
Three months	0,039	0,031	0,052	0,021	0,046	0,024	0,022174869
Four months	0,032	0,03	0,034	0,004	0,032	0,004	0,011087434
Five months	0,058	0,048	0,064	0,016	0,05	0,015	0,0294
Control	0,023	0,018	0,03	0,012	0,027	0,015	0,015714961
Placebo	0,02	0,016	0,029	0,013	0,022	0,01	0,011316065