



(86) Date de dépôt PCT/PCT Filing Date: 1999/09/10
(87) Date publication PCT/PCT Publication Date: 2000/03/23
(45) Date de délivrance/Issue Date: 2009/11/24
(85) Entrée phase nationale/National Entry: 2001/03/09
(86) N° demande PCT/PCT Application No.: EP 1999/006708
(87) N° publication PCT/PCT Publication No.: 2000/015273
(30) Priorité/Priority: 1998/09/11 (DE198 43 251.8)

(51) Cl.Int./Int.Cl. *A61L 27/34* (2006.01),
A61L 27/54 (2006.01), *A61L 27/58* (2006.01),
A61L 31/10 (2006.01), *A61L 31/14* (2006.01),
A61L 31/16 (2006.01)
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(54) Titre : IMPLANTS BIOLOGIQUEMENT ACTIFS RECOUVERTS D'UN POLYMERE BIODEGRADABLE
(54) Title: BIOLOGICALLY ACTIVE IMPLANTS COATED WITH A BIODEGRADABLE POLYMER

(57) **Abrégé/Abstract:**

The invention relates to an implant for providing pathological modifications on the spinal column and/or locomotor system. According to the invention, the implant comprises an enamel-type coating which has a thickness of 100 µm or less and which is made of a biodegradable polymer such as polylactide. This coating has an osteoinductive effect and thus an effect which promotes the healing of fractures. Additional osteoinductive materials such as growth factors can be incorporated in the coating. The invention also relates to a method for producing such an implant using the follow steps: Producing a dispersion of biodegradable polymers in an organic solvent; applying the dispersion to the surface to be coated; evaporating the solvent off.

**PCT**WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales BüroINTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation ⁷ : A61L 27/34, 27/54, 31/08, 31/16	A1	(11) Internationale Veröffentlichungsnummer: WO 00/15273 (43) Internationales Veröffentlichungsdatum: 23. März 2000 (23.03.00)
(21) Internationales Aktenzeichen: PCT/EP99/06708 (22) Internationales Anmeldedatum: 10. September 1999 (10.09.99) (30) Prioritätsdaten: 198 43 251.8 11. September 1998 (11.09.98) DE (71)(72) Anmelder und Erfinder: SCHMIDMAIER, Gerhard [DE/DE]; Claudiusstrasse 12, D-10557 Berlin (DE). RASCHKE, Michael [DE/DE]; Weddingen Weg 31, D-12205 Berlin (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): STEMBERGER, Axel [DE/DE]; Cramer-Klett-Strasse 35e, D-85579 Neubiberg (DE). (74) Anwalt: GLAWE, DELFS, MOLL & PARTNER; Rothenbaumchaussee 58, D-20148 Hamburg (DE).		(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Veröffentlicht <i>Mit internationalem Recherchenbericht.</i>
(54) Title: BIOLOGICALLY ACTIVE IMPLANTS (54) Bezeichnung: BIOLOGISCH AKTIVE IMPLANTATE (57) Abstract The invention relates to an implant for providing pathological modifications on the spinal column and/or locomotor system. According to the invention, the implant comprises an enamel-type coating which has a thickness of 100 μ m or less and which is made of a biodegradable polymer such as polylactide. This coating has an osteoinductive effect and thus an effect which promotes the healing of fractures. Additional osteoinductive materials such as growth factors can be incorporated in the coating. The invention also relates to a method for producing such an implant using the follow steps: Producing a dispersion of biodegradable polymers in an organic solvent; applying the dispersion to the surface to be coated; evaporating the solvent off. (57) Zusammenfassung Gegenstand der Erfindung ist ein Implantat zur Versorgung von pathologischen Veränderungen am Stütz- und/oder Bewegungsapparat. Erfindungsgemäß ist vorgesehen, daß es eine lackartige Beschichtung einer Stärke von 100 μ m oder weniger aus einem biologisch abbaubaren Polymer wie bspw. Polylactid aufweist. Diese Beschichtung weist eine osteoinduktive und damit die Frakturheilung fördernde Wirkung auf. Zusätzliche osteoinduktive Materialien wie Wachstumsfaktoren können in die Beschichtung eingearbeitet werden. Gegenstand der Erfindung ist ferner ein Verfahren zur Herstellung eines solchen Implantats, mit den Schritten: Herstellen einer Dispersion des biologisch abbaubaren Polymers in einem organischen Lösungsmittel; Aufbringen der Dispersion auf die zu beschichtende Oberfläche; Abdampfenlassen des Lösungsmittels.		

Biologically Active Implants Coated With A Biodegradable Polymer

This invention relates to an implant designed to compensate for pathological changes in the spinal column and/or locomotor system. The invention also covers a method for producing such an implant. Implants of the type mentioned have been part of prior art. They are intended, for instance, to mechanically stabilize a fracture, thus promoting the healing process or, in the case of endoprosthetic implants, to be permanently bonded to the bone.

For example, WO-A 9819699 describes the systemic administration of medications or hormones serving to promote osteosynthesis and thus to accelerate the healing process of the fracture. Examples of suitable means include growth factors such as IGF-I. Such systemic applications, however, can lead to undesirable side effects.

WO-A 9320859 describes the fabrication of a thin foil or film consisting of a polylactic-acid/polyglycol-acid copolymer containing growth factors. The intent is to wrap a foil of that type, for instance, around fracture-fixation devices prior to their application. This is supposed to release the growth factors in localized fashion in the area of the fracture. In practice, however, this method is unsuitable since, for instance, a nail wrapped with a foil of that type cannot be inserted in the medulla in a way that the foil, which only loosely

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envelops the nail, actually reaches the point of its intended healing action.

It is, therefore, the objective of this invention to provide an implant of the type mentioned first above, which promotes the healing process in pathological changes of the spinal column and locomotor system, especially by furthering an osteosynthesis, and thus accelerating the healing of fractures or the integration of an implant.

According to the invention this is accomplished, with this type of implant, by providing it with a varnish-like coating that is up to 100 μm thick and consists of a biodegradable polymer.

But first, a few definitions, used in describing this invention, need to be explained. The term *implant* refers to a device, which in the process of a surgical procedure is at least partially introduced inside the body. An implant of that type serves to support a pathologically changed spinal column and/or locomotor system, especially by providing a mechanical reinforcement. The pathological changes mentioned may be in the form of fractures, pathological changes of joints and bones, distended or torn ligaments or tendons and the like. A common feature in the novel implants consists of the fact that their application involves direct contact with attachment to or insertion in a bone of other part or element of the spinal column or locomotor system (such as ligaments or tendons).

The term *fracture fixation device* refers to any device that serves to fix, correct and/or

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mechanically stabilize a fractured bone. Examples thereof include plates, screws, nails, pins, wires, sutures or cages for the spinal column and locomotor system. As a rule, fracture fixation devices of that nature are removed after the fracture has healed, but in certain circumstances, they may be permanently left in or on the bone or they can be reabsorbed by the organism.

Endoprosthetic implants are designed to permanently remain in the body and usually function as substitutes for a natural body part such as a joint, a bone section or a tooth.

The term *implant* is to be understood in the broadest sense of the word since it also includes, for instance, implants which are used for elongative or reductive ostectomies, craniotomies, for ligament healing and restoration, for tumor and sports-injury-related surgery, in dentistry as well as in the case of oral, maxillary and facial dislocations.

The implants are produced from a base material that is chemically and/or physically different from that of the varnish-like coating. In many cases the base material will not be biodegradable. This implies that under the conditions prevailing in the location of the body, where it is used and for the length of time during which it is typically retained in the body, it must not decay, corrode or in any other way, change its physiochemical state or, if at all, then only with a negligible deterioration of its desired effect. An implant according to the invention will in many cases consist of a metal or an alloy such as stainless steel or titanium. Alternatively, the implant may consist of a base material which is itself biodegradable or bioresorbable without, however,

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offering the beneficial properties described below unless provided with the varnish-like coating per this invention.

According to the invention, the implants are provided with a varnish-like coating. The term *varnish-like* means that the coating bonds with the surface of the base material with enough adhesive strength that, when the implant is applied, mechanical friction will not abrade or otherwise damage the coating, or at least, not to such an extent as to compromise its physical effect, described in more detail further below. For example, it must be possible to properly drive a nail, provided with the varnish-like coating, into the bone without any significant abrasion of the varnish-like coating.

The coating is up to 100 μm thick. In other words, the average thickness of the coating is 100 μm or less. The invention allows for spots with a thickness of more than 100 μm occasioned by fluctuations in the coating process.

The coating consists of a biodegradable polymer. This means that, due to its exposure to the physiological conditions prevailing in the area of the implant, it will progressively degrade, over a period of preferably several weeks or months, through molecular breakdown. These molecular separation products and any other metabolites preferably display no or, at worst, only negligible toxicity and the body should be able to metabolize or excrete all or most of them. Polymers, which contain no toxic metabolites

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and can be completely biodegraded and eliminated, are also referred to as *bioresorbable*. The polymers used in applying this invention are preferably of the bioresorbable type.

The invention is based on the surprising realization that, even without the addition of other pharmaceutically active agents such as growth factors, a varnish-like coating, according to this invention, has an osteosynthesizing and thus contributory fracture-healing and even infection-fighting and thus complication-avoiding effect.

The thickness of the varnish-like coating is preferably 50 μm or, better, about 30 μm and most preferably about 20 μm or less. In many cases, the preferred thickness is between 10 and 30 μm and most desirably between 10 and 20 μm .

The polymer employed has preferably a glass transition temperature of 37°C (98.6°F) or higher so as to retain its desired strength in the body. Within the scope of this invention, polymers with a mean molecular weight of 100 kDa or less are preferred.

The polymer is preferably selected from among the group comprising poly- α -hydroxy acids, polyglycols, polytyrosine carbonates, starch, gelatins, cellulose as well as blends and interpolymers containing these components. Particularly preferred among the poly- α -hydroxy acids are the polylactides, polyglycol acids and their interpolymers. One example of a suitable polylactide is marketed by Boehringer-Ingelheim under the trade name R 203. It is a racemic poly-D,L-lactide. This racemic compound forms an amorphous, varnish-like layer on the surface of the implant. The formation of crystalline polymer

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structures in the coating should preferably be avoided, which is why an enantiomerically pure lactide is not normally used. Suitable polytyrosene carbonates include for instance p(DTE-co-5% PEG 1000 carbonates) and p(DTE-co-26% PEG 20000 carbonates). These are copolymers containing the specified amounts of polyethylene glycols.

Within the scope of this invention, the coating can contain additional pharmaceutically active agents, such as osteoinductive or biocidal or anti-infection substances. Suitable osteoinductive substances include, for instance, growth factors whose proportion of the total weight of the coating is preferably 0.1 to 10% by weight or, better, 0.5 to 8% by weight and, most desirably, 1 to 5% by weight. This weight percentage relates to the net amount of the active agent, without counting any pharmaceutical carrier substances.

The growth factors may be selected from the group of IGF (insulin-like growth factors), TGF (transforming growth factors), FGB (fibroblast growth factors), EGF (epidermal growth factors), BMP (bone morphogenic proteins) and PDGF (platelet-derived growth factors). These growth factors are well known to the expert and are commercially available.

The varnish-like coating preferably contains the IGF-I or TGF- β growth factors, with particular preference given to a combination of these two growth factors.

This invention also relates to a method for producing an implant of the type described

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above, along these steps:

- Preparing a dispersion of the biodegradable polymer in an organic solvent;
- Applying the dispersion on the surface to be coated;
- Allowing the solvent to evaporate.

The term dispersion refers to any given distribution of the polymer in an organic solvent. This may be a chemical solution, a purely physical dispersion or any intermediate step, especially including for instance, colloidal solutions.

The application of the dispersion and the evaporation of the solvent preferably take place at a temperature of between 0 and 30°C (32 - 86°F), and more desirably at a room temperature of about 22°C (72°F). This so-called cold coating also allows for temperature-sensitive components such as certain growth factors to be applied on the implant together with the polymer. The application is performed preferably by immersing the implant in the dispersion. Other ways of applying the coating, for instance by brushing, spraying etc., are also possible. Of course, in addition to the polymer, the dispersion can also contain the aforementioned pharmaceutically active agents such as osteoinductive or biocidal substances.

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Most preferably, the solvent is allowed to evaporate in a gas atmosphere, essentially saturated with solvent vapor. To that end, it is desirable to manipulate the implant that has been immersed in the dispersion, in a closed space whose atmosphere is highly solvent-saturated. This will result in a very slow evaporation of the solvent, and consequently, in a uniform, well-adhering varnish-like coating. The preferred evaporation time is between 1 minute and 1 hour, or better, 5 to 30 minutes and most desirably about 10 minutes.

It is also preferred to apply the coating by incrementally building it up in several thin layers, for which purpose the application of the dispersion and the solvent-evaporation process are repeated twice or perhaps several times.

Particular preference within the scope of this invention is given to the use of a dispersion, which is constituted by a colloidal solution of the polymer in the solvent. This colloidal solution preferably contains colloidal polymer particles between 1 and 1000 nm and preferably less than 400 - 500 nm in size. For example, this type of colloidal solution can be produced by mixing the polymer and the solvent, then letting it stand for a period of 1 minute to 24 hours, preferably 2 to 24 hours, more preferably 3 to 12 hours, better yet 8 hours, and most desirably about 6 hours. During the most preferred period of about 6 hours, polymer colloid particles will form in the desired size range of less than about 500 nm.

To separate any remaining larger polymer particles, the colloidal solution can be filtered prior to its application on the implant, preferably by using a micropore filter whose

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pore size corresponds to the desired maximum size of the colloid particles. Micropore filters are commercially available with pore sizes for instance of 0.45 or 0.2 μm .

The solvents used are preferably popular organic, nonpolar or weakly polar solvents. Particular preference within the scope of this invention is given to ethyl acetate or chloroform.

Prior to its application on the implant, the dispersion contains an amount of preferably 20 to 300 mg, and more desirably 50 to 150 mg, of polymer (perhaps including other constituents such as osteoinductive or biocidal substances) per ml of solvent.

The following will explain the invention by means of implementation examples with the aid of the drawings in which:

Fig. 1 shows the biodegradation of a polylactide coating on an implant per this invention as a function of time both in vivo and in vitro;

Fig. 2 illustrates the release of the growth factors contained in the polylactide coating as a function of time;

Fig. 3 shows a radiographic comparison of the effect of implants coated per this invention versus untreated (uncoated) implants on fracture healing in rats;

Fig. 4 shows a biomechanical comparison of these implants;

Fig. 5 shows a histomorphometric comparison of these implants;

Fig. 6 shows illustrations of histomorphometric examinations;

Fig. 7 shows a radiographic comparison between coated and uncoated implants in Yucatan pigs;

Fig. 8 is a biomechanical comparison of the corresponding implants per fig. 7;

Fig. 9 shows the maximum torsional load and torsional stiffness in another examination of tibia fractures in rats.

Example 1: Producing an implant according to this invention

400 mg PDLLA (poly(D,L) lactide, Resomer™ R 203 by Boehringer-Ingelheim) is dispersed in 6 ml chloroform at room temperature. If the coating is to contain other osteoinductive or biocidal substances, these are also added to the dispersion, in which case 400 mg is the total combined weight of the PDLLA and the additives.

The dispersion is allowed to sit for 6 hours until a colloidal solution has formed, which is then passed through a sterile microfilter with a pore size of 0.45 µm into a sterile container.

Next, Kirschner wires (1.6 mm in diameter, 3.5 cm long) of titanium and steel as well as titanium bone nails are immersed in the filtered solution, whereupon the solvent is

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allowed to evaporate in a chloroform atmosphere for a period of 10 minutes. This process (coating and evaporation) is repeated once.

The implants obtained will be coated with a thin, varnish-like polymer layer about 10 to 20 μm thick.

Example 2: Microbiological properties of the coating

After an incubation time of respectively 6 weeks and 12 weeks, microbiological examinations of titanium Kirschner wires coated with a layer of PDLLA per this invention revealed no noticeable growth of microorganisms.

Additionally, ten implants coated with PDLLA per this invention and ten uncoated implants were each contaminated with staphylococci ($\text{KD } 10^5$). The coated implants displayed a significantly lower adhesion rate of these microorganisms.

Example 3: Mechanical strength of the coating

20 titanium and steel Kirschner wires each were weighed and then coated, as in Example 1, with PDLLA containing 1% methyl violet as color marker.

The wires were implanted in the tibiae of rats. Following explantation, the mechanical abrasion of the coating was measured by weighing and by photometric analysis. The highest abrasion rate found was 2.9% in the case of titanium wires and 4.6% for steel wires. Raster electron micrographs showed that in none of the implants examined

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had the coating been abraded all the way to the metal surface.

Example 4:

This example will show the advantages of a colloidal solution for the mechanical strength of the coating.

800 mg each of PDLLA R 203 was added to 2 batches of 6 ml ethyl acetate each. The resulting dispersions were allowed to sit at room temperature for 6 and, respectively, 24 hours and were then filtered as in Example 1. The dispersions or solutions thus obtained were used to coat so-called stents, employing the procedure per Example 1. It should be mentioned that stents are not implants of the type covered by this invention. They were used only because they are particularly well suited to the performance of elongation tests and thus to the analysis of the mechanical strength of the varnish-like coating.

The volume of the coating was determined by weighing the stents before and after the application of the coating.

In the manner with which the expert is familiar, the coated stents were expanded with a PTCA balloon at a pressure of 8 bar (116 psi). The expanded stents were weighed again to determine the amount of the coating material that had peeled off or was lost some other way.

It was found that the stents which were coated with the dispersion that had stood for 6 hours prior to the filtering had lost an average of 0.8% of their coating while the other

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stents (which had stood for 24 hours) had a loss of 6.0% by weight. This indicates that for mechanical strength of the coating it is better not to produce a complete chemical polymer solution in the solvent, but rather, a colloidal solution with a colloidal particle size of 0.45 μm or less.

Example 5: Stability of the active agents contained in the coating

To determine the stability of the growth factors (WF) incorporated in the coating, titanium Kirschner wires were coated with PDLLA as in Example 1, containing the growth factors IGF-I (5% by weight) and TGF- β I (1% by weight). The stability (storage life) of the growth factors was analyzed after 6 weeks, 6 months and 1 year. After 6 weeks, the loss in effectiveness was found to be less than 3%. After 6 months, the growth factors included in the coating were found to be still better than 95.5% effective; and after 1 year better than 93%. This proves that the active agents, incorporated in the coating as provided for by the invention, retain their biological stability and effectiveness even if the coated implant is stored for an extended period of time before it is used.

Example 6: Biodegradation of the PDLLA coating

Titanium Kirschner wires, coated with PDLLA per Example 1, were subjected to in-vitro elutriation tests. To simulate in-vivo situations, the elutions were passed through a

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physiological 0.9% NaCl solution at a temperature of 37°C (98.6°F) under laminar air-flow conditions.

Within 9 weeks about 10% of the PDLLA coating had progressively degraded.

For an in-vivo study of the biodegradation characteristics of the PDLLA coating, 10 PDLLA-coated Kirschner wires with a defined coating volume were implanted in Sprague Dawley rats. After 6 weeks, the implants were removed and the in-vivo degradation of the PDLLA coating was determined by measuring the difference between the pre-implantation and the post-explantation weight, as well as the inherent viscosity, and the molecular weight of the completely separated coating, followed by a comparison with the in-vitro data.

The result can be seen in Fig. 1. Within 9 weeks, about 10% of the PDLLA coating had biodegraded. The comparative in-vivo measurement shows that at that point in time, the in-vitro and in-vivo results were fairly identical.

Example 7: Examination of the release of active agents integrated in the coating

As in Example 1, titanium Kirschner wires were coated with PDLLA, which additionally contained either 5% by weight of IGF-I or 1% by weight of TGF- β 1 or a combination of 5% by weight of IGF-I and 1% by weight of TGF- β 1.

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The release pattern of the growth factors incorporated in the coating was analyzed by means of in-vitro elutriation tests. The results are shown in Fig. 2. Within 48 hours, an initial release of growth factors from the coating took place at a rate of 48 to 54%. From there, the release continued progressively until after 6 weeks, a total of between 71 and 78% of the growth-factor inclusions were released.

10 titanium Kirschner wires, coated with PDLLA and the above-mentioned growth factors, were implanted in the tibiae of each of the Sprague Dawley rats used. After 42 days, the implants were removed and the residual concentrations of the growth factor inclusions were measured, using ELISA. As can be seen in fig. 2, the in-vivo results matched those of the in-vitro elutriation tests.

Example 8: Osteoinductive effect of the implants per this invention

In an experiment with animals, tests were conducted on 60 such animals (5-months-old female Sprague Dawley rats).

All test animals were subjected to a standardized fracture of the right tibia. Differently coated titanium wires (1.0 mm in diameter) were then implanted in the repositioned tibiae as intramedullary supports.

Postoperatively, each day up to the 42nd day depending on group assignment (see below), 2 mg/kg of a rat-specific recombinant growth hormone (r-rGH) or, respectively, a placebo was subcutaneously injected. At the points in time 0 d, 4 d, 7 d, 14 d, 21 d,

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28 d, 35 d and 42 d, after administration of an anaesthetic inhalant, x-rays were taken in two planes, 1.25 ml of blood was taken from each, by the retrobulbar method (deep-frozen at -80°C (-112°F)), and their weight and body temperature were measured. On day 42, the fractured and the unfractured tibiae, along with the periosteum, were separately prepared and subjected to biomechanical tests (torsional load - torsional stiffness).

Group assignments

- Group I: Fracture of the right tibia - uncoated implant -
 Systemic application of a placebo (control group)
- Group II: Fracture of the right tibia - implant coated with poly-D,L-lactide ® 203) -
 Systemic application of a placebo
- Group III: Fracture of the right tibia - implant coated with poly-D,L-lactide -
 Systemic application of (r-rGH)
- Group IV: Fracture of the right tibia - implant coated with
 poly-D,L-lactide and growth factors IGF-I (5%) and TGF- β (1%) -
 Systemic application of a placebo
- Group V: Fracture of the right tibia - implant coated with
 poly-D,L-lactide and growth factors IGF-I (5%) and TGF- β (1%) -
 Systemic application pf (r-rGH)

The coated implants were produced as indicated in Example 1.

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Results:**Fracturing**

The fracturing model employed lent itself well to the creation of a standardized transverse fracture of the right tibia, without any major damage to the soft tissue. In 2 out of 60, the tibia fracture was comminuted; in one, it was helical, requiring premature discontinuation. One animal died in a postoperative examination under anesthesia (32nd day).

Weight and temperature

In the animals systemically treated with (r-rGH) (Groups III and V), there was no rise in body temperature during the course of the test, in comparison to the animals that had been given a placebo (Groups I, II and IV), but their body weight increased significantly by 13% ($p < 0.05$). No major differences were found among Groups I, II and IV (placebo) or III and V (GH).

Biomechanical test

The data obtained are expressed in absolute values (torsional load) and in percentages (torsional stiffness), as compared to the unfractured opposite side.

The results reveal a significant increase ($p < 0.05$) of the maximum torsional load in Group III, as well as Groups IV and V, as compared to the systemic application. It appears that the local application of growth factors (Group IV) not only leads to a markedly higher maximum torsional load, compared to the control group, but on

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average also when compared with the results of the systemic application of r-rGH (insignificant). No further increase in the maximum torsional load was observed as a result of simultaneous administration of r-rGH and the local application of IGF-I and TGF- β . The maximum torsional load in the group treated with poly-D,L-lactide increased significantly, compared to that of the control group.

In terms of torsional stiffness, relative to that of the contralateral tibia, comparable findings were made. In this case as well, the groups, with the local application of growth factors, showed the most favorable results.

Fig. 9 summarizes these results.

Example 9:

5 months-old female Sprague Dawley rats (n=144) were subjected to a standardized closed fracture of the right tibia using a fracturing machine; and uncoated versus coated titanium Kirschner wires were implanted in the tibiae as intramedullary stabilizers. A comparison was made between the following groups:

- Group I: Uncoated implant (control group)
- Group II: Implant coated with PDLLA ® 203)
- Group III: Implant coated with PDLLA + r-IGF-I (5%)

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Group IV: Implant coated with PDLLA + r-IGF-I (5%) + TGF- β 1 (1%)

The coated implants were produced as in Example 1.

Time-sequential radiographs were taken in 2 planes (a.-p. and lateral). At time points 0 d, 4 d, 7 d, 14 d, 21 d, 28 d, sera were measured, including the systemic concentration of r-IGF-I and r-TGF- β 1 and the body weight and body temperature were determined. After 4 weeks, the implants were removed and the fractured tibiae were biomechanically tested in comparison with the untreated contralateral tibiae. The histomorphometric examination (O. Safranin/v.Kossa) of the calli was quantified by means of an analytical imaging system (Zeiss KS 400).

In the radiographic evaluation, the untreated Group I still showed a distinct fractured dissociation. Groups II and III displayed good callus formation, as compared to the uncoated Group I. In the animals of Group IV, the fractures had almost completely consolidated (Fig. 3).

Compared to the untreated contralateral tibia, and in a comparison with all other groups, the biomechanical tests revealed for Group IV a significantly higher maximum torsional load and maximum torsional stiffness. The combined application of r-IGF-I and r-TGF- β 1 produced a substantially higher maximum torsional load and maximum torsional stiffness, compared to the group treated with IGF-I.

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The group treated with polylactide showed a significantly higher maximum torsional load and maximum torsional stiffness than the untreated Group I (Fig. 4).

The histomorphometric examinations substantiate the radiographic and biomechanical test results. There were substantially more areas of connective tissue cells in Group I than in the treated groups. The group treated with PDLLA displayed good callus formation and a pattern of advanced callus reconstruction, with a minimal proportion of connective tissue cells. Group IV displayed an almost completely restored fracture and the highest bone density in the callus. The group treated with polylactide only also showed a significantly higher bone density in the callus area, as compared with the control group (Fig. 5 and 6).

Between the treated and the untreated groups, no changes were evident in terms of serum parameters, body weight or body temperature.

Example 10:

12 months-old Yucatan dwarf pigs (n=30) were subjected to a standardized osteotomy (1 mm gap) of the right tibia which was then intramedullarily stabilized with coated and, respectively, uncoated titanium tibia nails and statically locked. A comparison of the following groups was made:

Group I: Uncoated implant (control group)

Group II: Implant coated with PDLLA ® 203)

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Group III: Implant coated with PDLLA + r-IGF-I (5%) + TGF- β 1 (1%)

The coated implants were produced as in Example 1.

Time-sequential radiographic examinations and serum tests were performed. After 4 weeks, the two tibiae were removed and biomechanically tested. The callus diameter was measured and the callus volume was determined by the Archimedes principle.

Results:

After 4 weeks, all of the control-group animals showed an incomplete consolidation of the osteotomy gap. The group treated with polylactide showed good callus formation. Group III displayed substantially advanced callus formation (Fig. 7).

In Group II, treated with polylactide, and Group III, additionally treated with growth factors, the callus volume and callus diameter were significantly greater than in the control group.

Compared to the contralateral tibia, and in comparison with the control group, the group treated with polylactide displayed a considerably higher maximum torsional load and maximum torsional stiffness.

The inclusion of growth factors in the polylactide coating produced a significant

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augmentation of the maximum torsional load and maximum torsional stiffness.

Strength of the intramedullary support

The standardized explantation of the titanium wires from the tibiae, using a power extractor, required substantially more extractive force for explanting the wires coated with IGF-I and TGF- β than those in the control group.

It is evident from the Examples 8 to 10 that the use of an implant, coated in accordance with this invention, can significantly accelerate the osteosynthesis and thus the healing process of the fracture. This accelerated process has been documented for a polymer-coated implant, without the addition of other osteoinductive agents. Incorporating growth factors in the coating permits a further acceleration of the fracture-healing process, with the combined application of IGF-I and TGF- β being particularly effective.

The examples also show that by means of the method per this invention, it is possible to produce a varnish-like coating, which by virtue of its physical structure and mechanical strength clearly distinguishes itself from any prior art.

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Abbau	=	Breakdown
Zeit	=	Time
Freisetzung	=	Release

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unbeschichtet	=	uncoated
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Maximales Drehmoment	=	Maximum torsional load (maximum torque)
leer	=	empty
Torsionale Steifigkeit	=	Torsional stiffness (rigidity)

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Implant serving to compensate for pathological changes in the spinal column and/or locomotor system, characterized in that it is provided with a varnish-like biodegradable polymer coating with a thickness of 100 μm or less, wherein the varnish-like coating bonds with a surface of a base material with enough adhesive strength that, when the implant is applied, mechanical friction will not abrade the varnish-like coating, and the varnish-like coating is producible by a method consisting of the following steps:
 - preparing a dispersion of the biodegradable polymer in an organic solvent;
 - applying the dispersion on the surface to be coated;
 - allowing the solvent to evaporate in a gaseous atmosphere, saturated with solvent vapor.
2. Implant as in claim 1, characterized in that it is selected from the group comprised of fracture-fixation and endoprosthetic devices.
3. Implant as in claim 2, characterized in that the fracture-fixation device is selected from the group comprised of plates, screws, nails, pins, wires, threads, and cages, used for the spinal column and locomotor system.
4. Implant as in one of the claims 1 to 3, characterized in that the varnish-like coating has a thickness of 50 μm or less.
5. Implant as in one of the claims 1 to 3, characterized in that the varnish-like coating has a thickness of 30 μm or less.
6. Implant as in one of the claims 1 to 3, characterized in that the varnish-like coating has a thickness of 20 μm or less.
7. Implant as in claim 4, characterized in that the varnish-like coating has a

thickness of 10 to 30 μm .

8. Implant as in claim 4, characterized in that the varnish-like coating has a thickness of 10 to 20 μm .
9. Implant as in one of the claims 1 to 8, characterized in that the polymer has a glass transition temperature of 37°C or higher.
10. Implant as in one of the claims 1 to 9, characterized in that the mean molecular weight of the polymer is 100 kDa or less.
11. Implant as in one of the claims 1 to 10, characterized in that the polymer is selected from the group comprised of poly- α hydroxy acids, polyglycols, polytyrosine carbonates, starch, gelatins, cellulose, and blends and interpolymers thereof.
12. Implant as in claim 11, characterized in that the poly- α hydroxy acids are selected from the group comprised of polylactides, polyglycol acids and interpolymers thereof.
13. Implant as in one of the claims 1 to 10, characterized in that the varnish-like coating further contains pharmaceutically active additives.
14. Implant as in claim 13, characterized in that the pharmaceutically active additives contain osteoinductive substances.
15. Implant as in claim 14, characterized in that the osteoinductive substance further contains one or more growth factors.
16. Implant as in claim 15, characterized in that the growth-factor percentage of the coating is 0.1 to 10% by weight.
17. Implant as in claim 15, characterized in that the growth-factor percentage of the coating is 0.5 to 8% by weight.

18. Implant as in claim 15, characterized in that the growth-factor percentage of the coating is 1 to 5% by weight.
19. Implant as in claim 15, characterized in that the growth factors are selected from the group comprised of IGF, TGF, FGF, EGF, BMP, and PDGF.
20. Implant as in claim 15, characterized in that the varnish-like coating further contains IGF-I and/or TGF- β .
21. Implant as in claim 15, characterized in that the varnish-like coating further contains a combination of IGF-I and TGF- β .
22. Method for producing the implant per one of the claims 1 to 21, consisting of the following steps:
 - preparing a dispersion of a biodegradable polymer in an organic solvent;
 - applying the dispersion on a surface to be coated;
 - allowing the solvent to evaporate in a gaseous atmosphere, saturated with solvent vapor.
23. Method as in claim 22, whereby the application and evaporation processes take place at a temperature of between 0 and 30°C.
24. Method as in claim 22, whereby the application and evaporation processes take place at a temperature of about 22°C.
25. Method as in claim 22, 23 or 24, whereby the application of the dispersion and the evaporation of the solvent are repeated two or more times.
26. Method as in one of the claims 22 to 25, whereby the dispersion is a colloidal solution of the polymer in the solvent.
27. Method as in claim 26, whereby the colloidal solution is produced by allowing

a mixture of polymer and solvent to stand for 1 minute to 24 hours.

28. Method as in claim 26, whereby the colloidal solution is produced by allowing a mixture of polymer and solvent to stand for 2 to 24 hours.
29. Method as in claim 26, whereby the colloidal solution is produced by allowing a mixture of polymer and solvent to stand for about 6 hours.
30. Method as in claim 26, 27, 28 or 29, whereby the colloidal solution is filtered prior to its application.
31. Method as in claim 30, whereby the colloidal solution is filtered through a micropore filter with a pore size of 0.45 μm or smaller.
32. Method as in one of the claims 22 to 31, whereby ethyl acetate or chloroform is used as the solvent.
33. Method as in one of the claims 22 to 32, whereby the dispersion contains 20 to 300 mg of polymer per ml of solvent.
34. Method as in one of the claims 22 to 32, whereby the dispersion contains 50 to 150 mg of polymer per ml of solvent.

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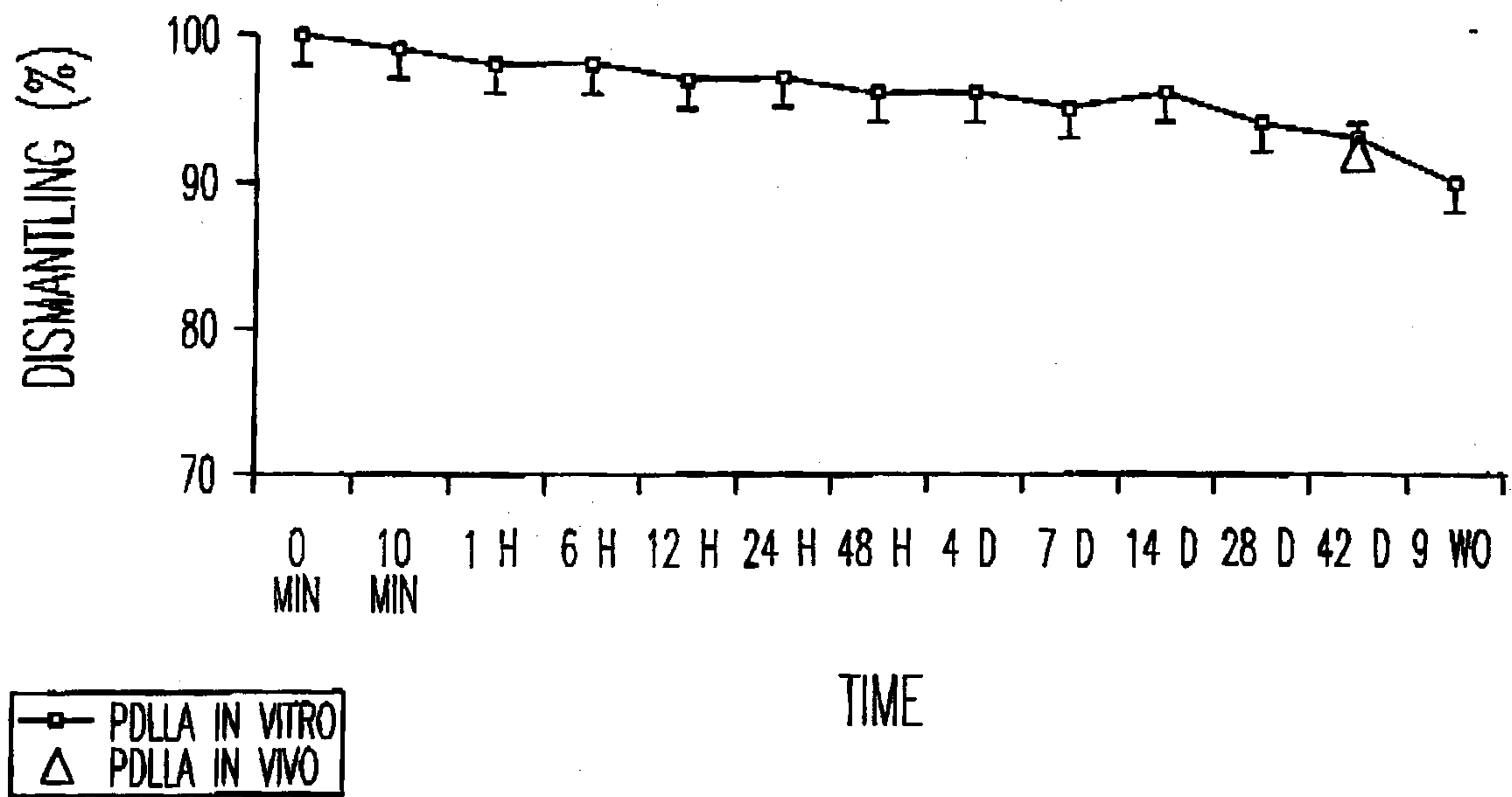


Fig. 1

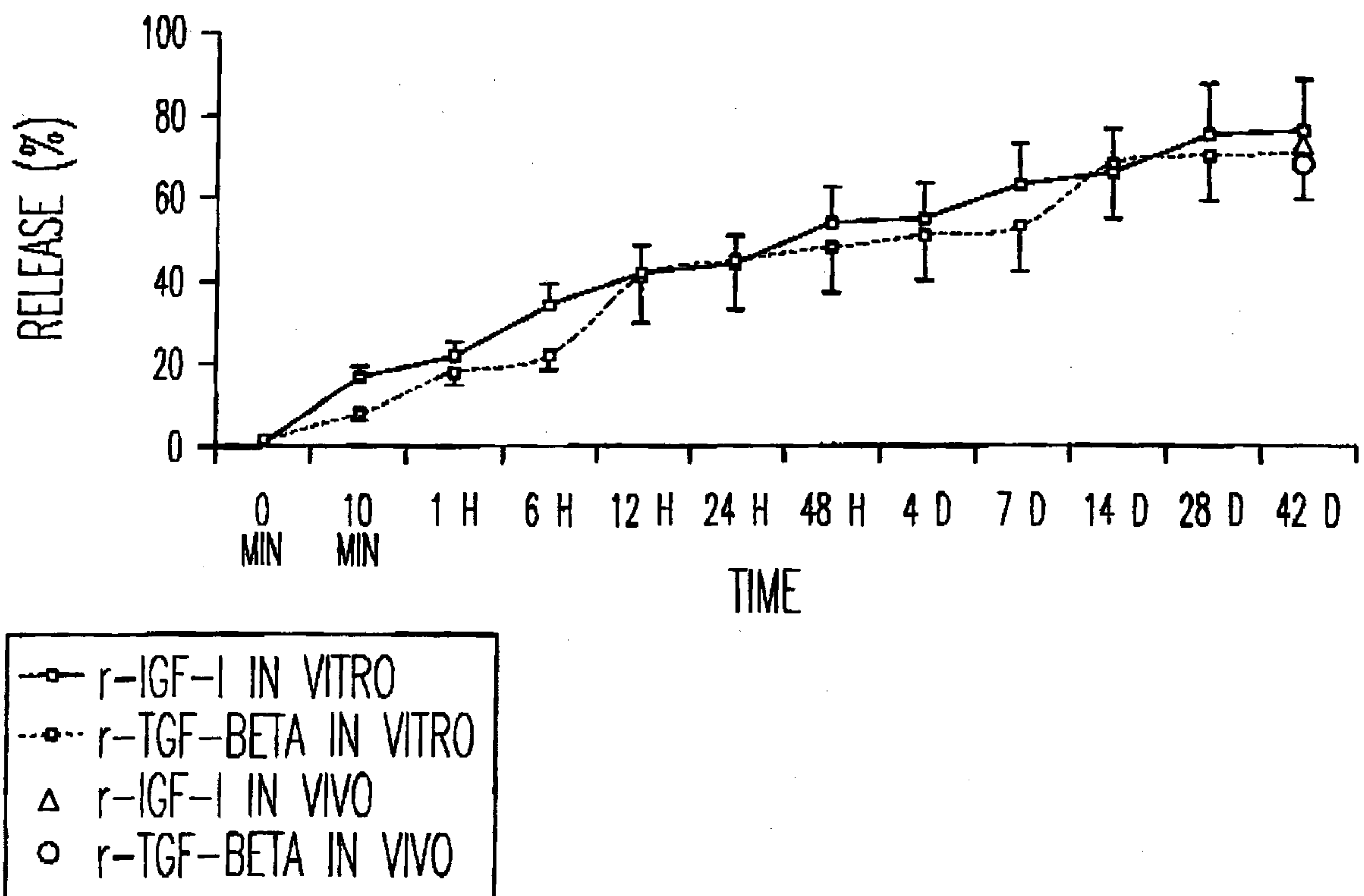
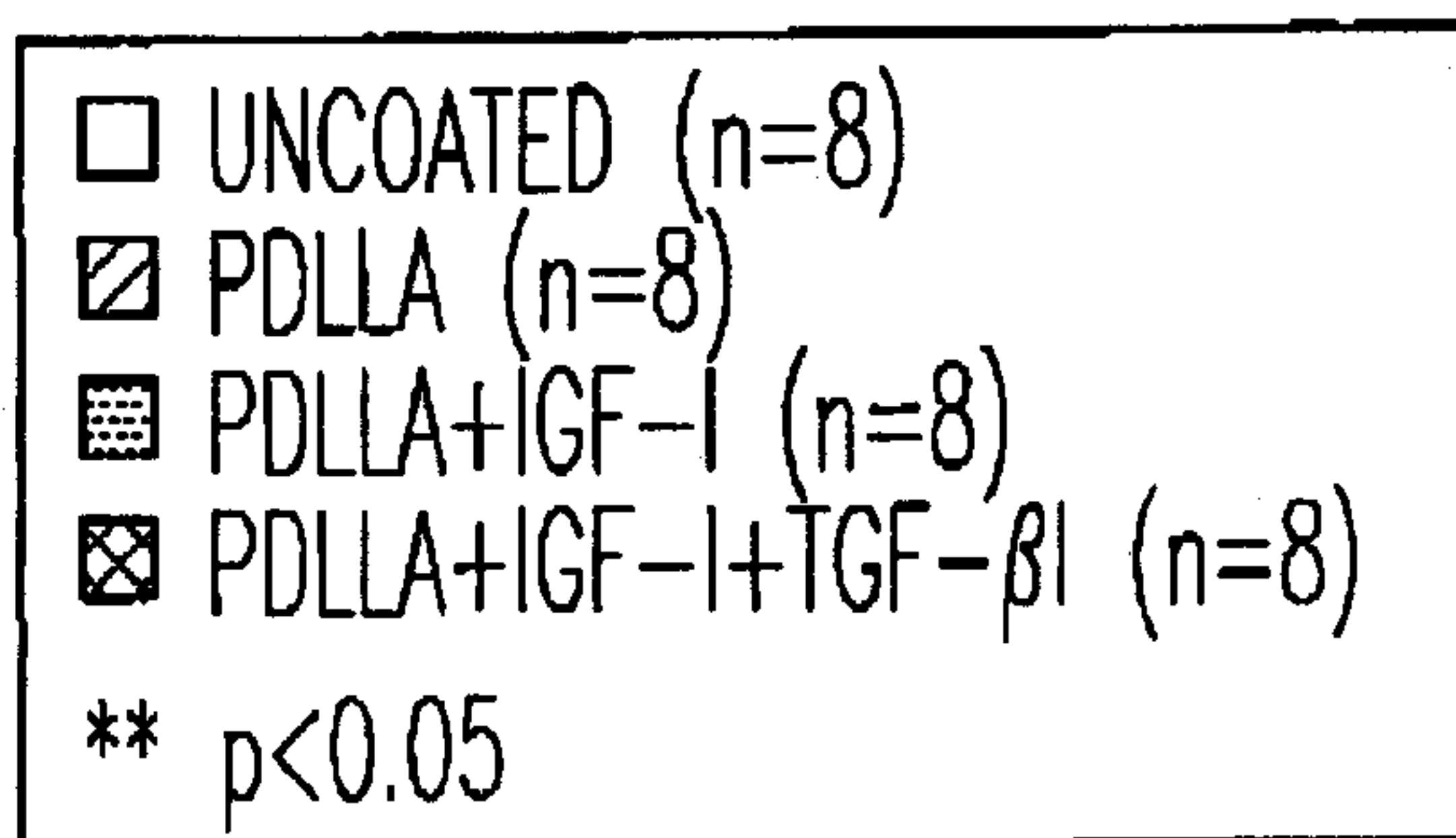
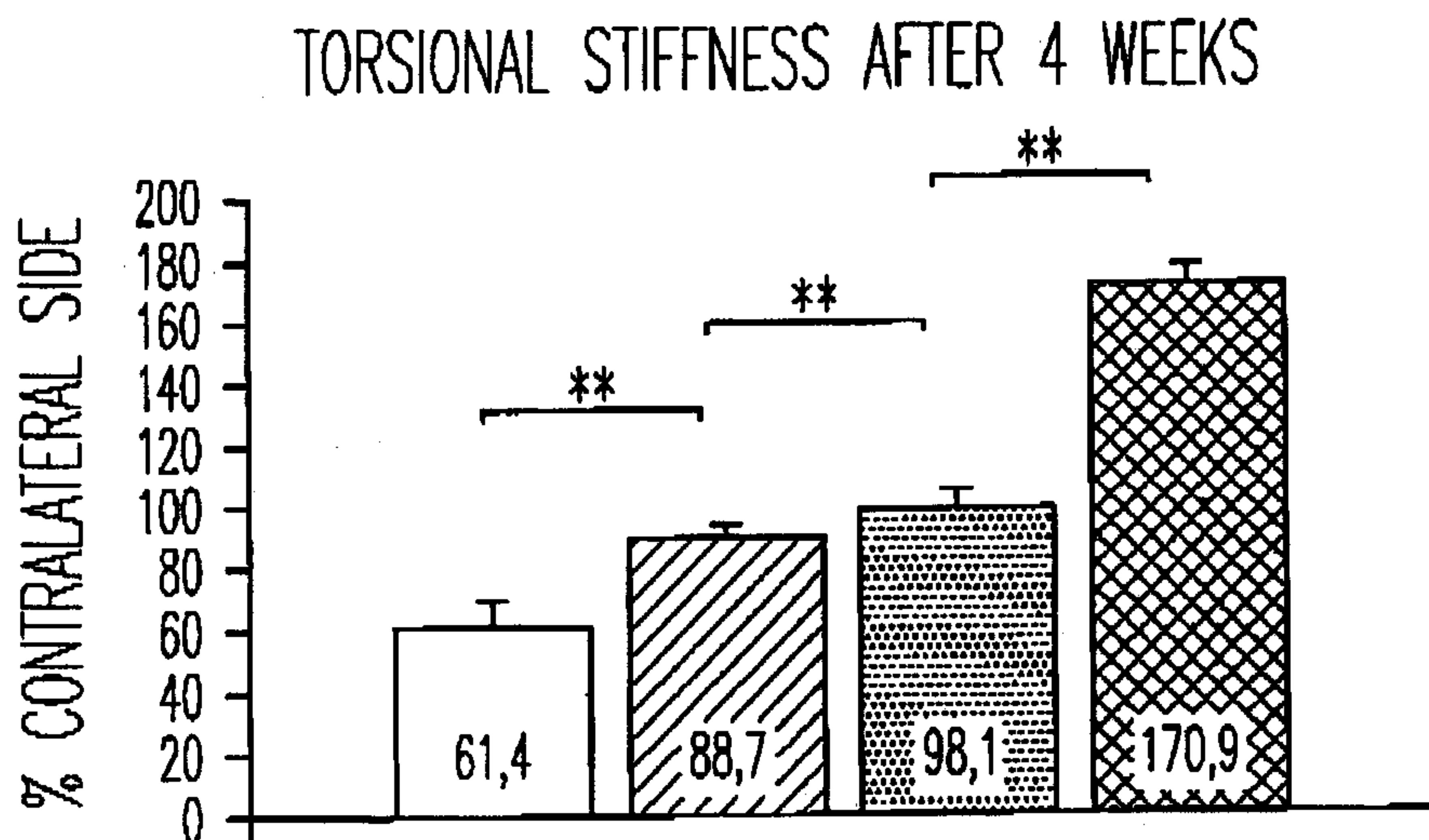
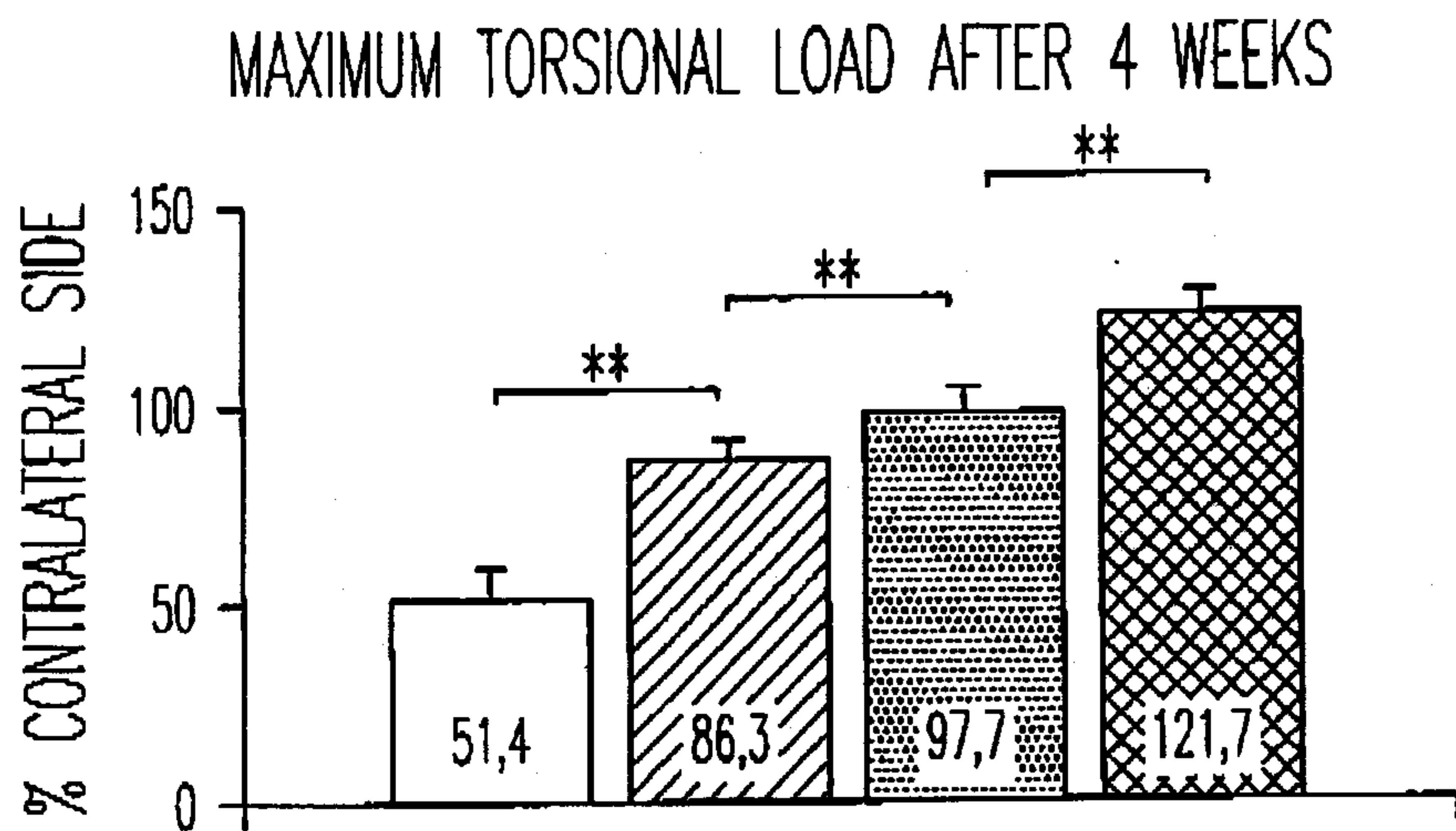


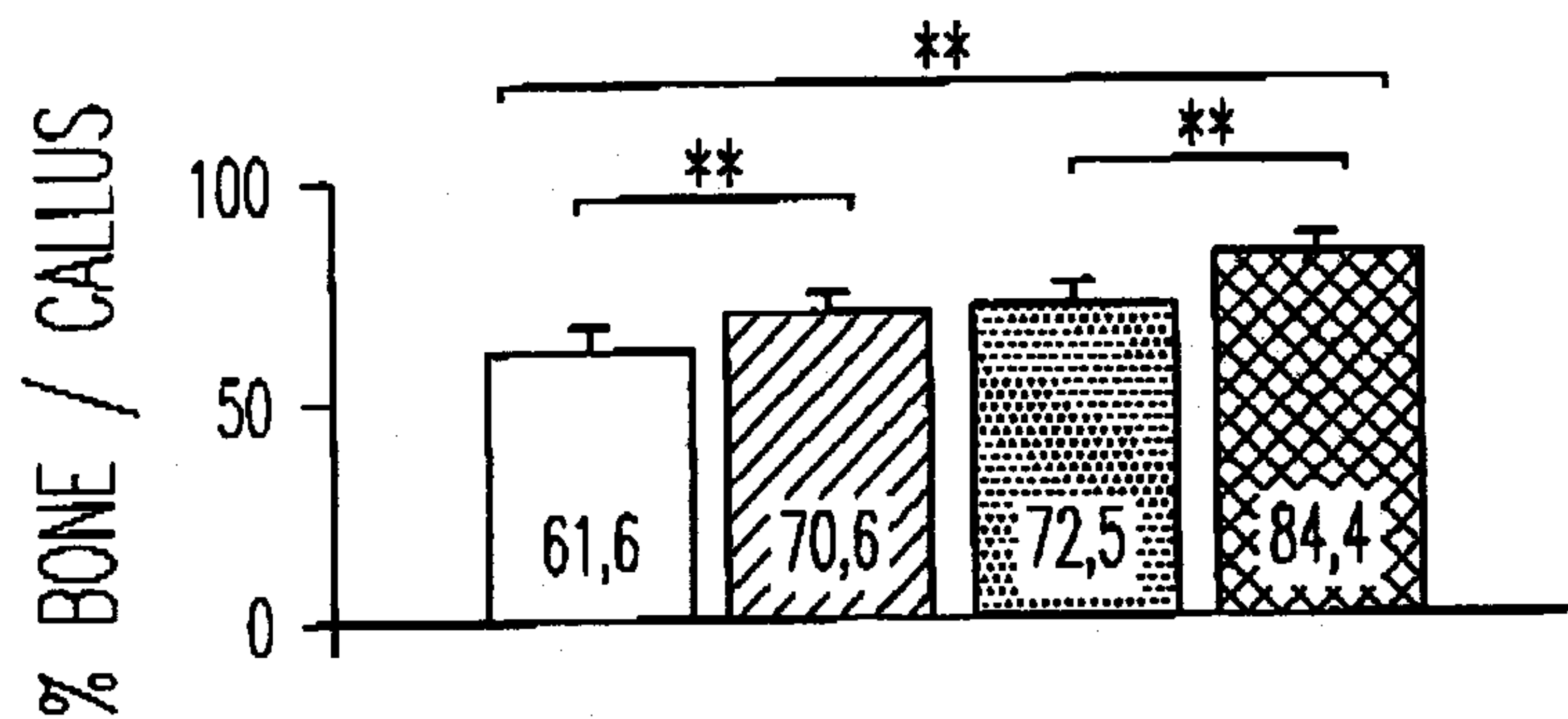
Fig. 2

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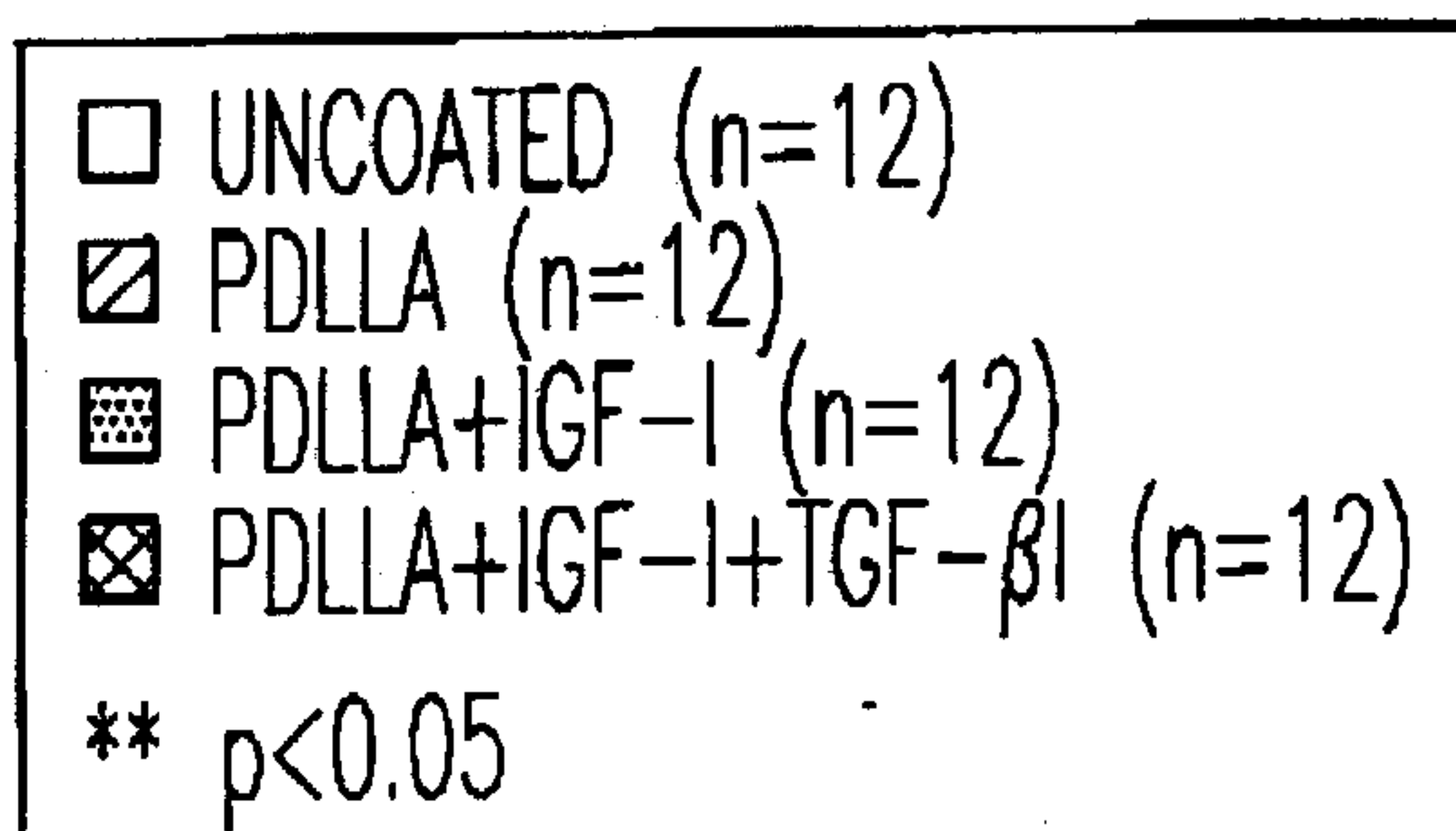
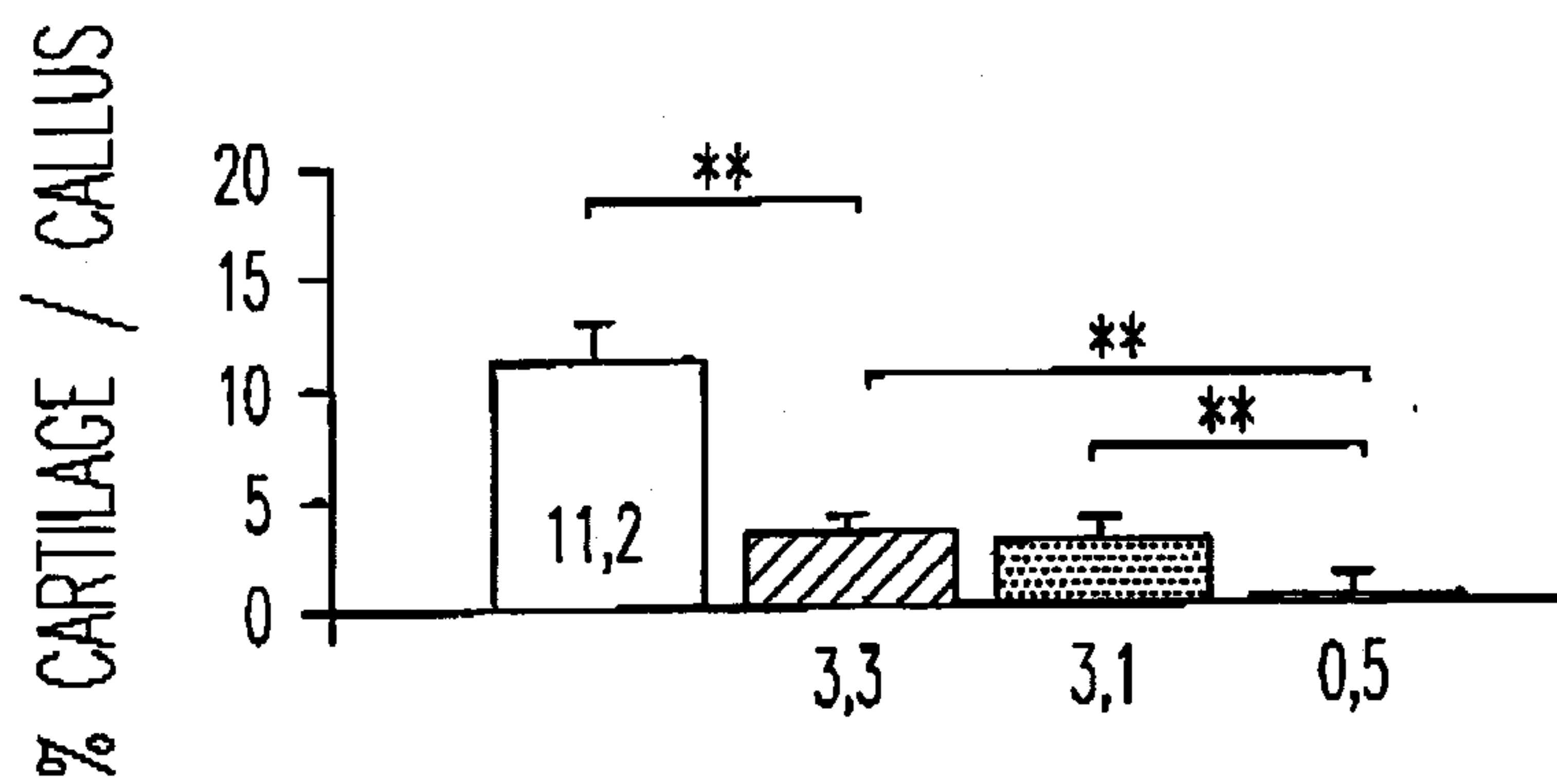
*Fig. 4*

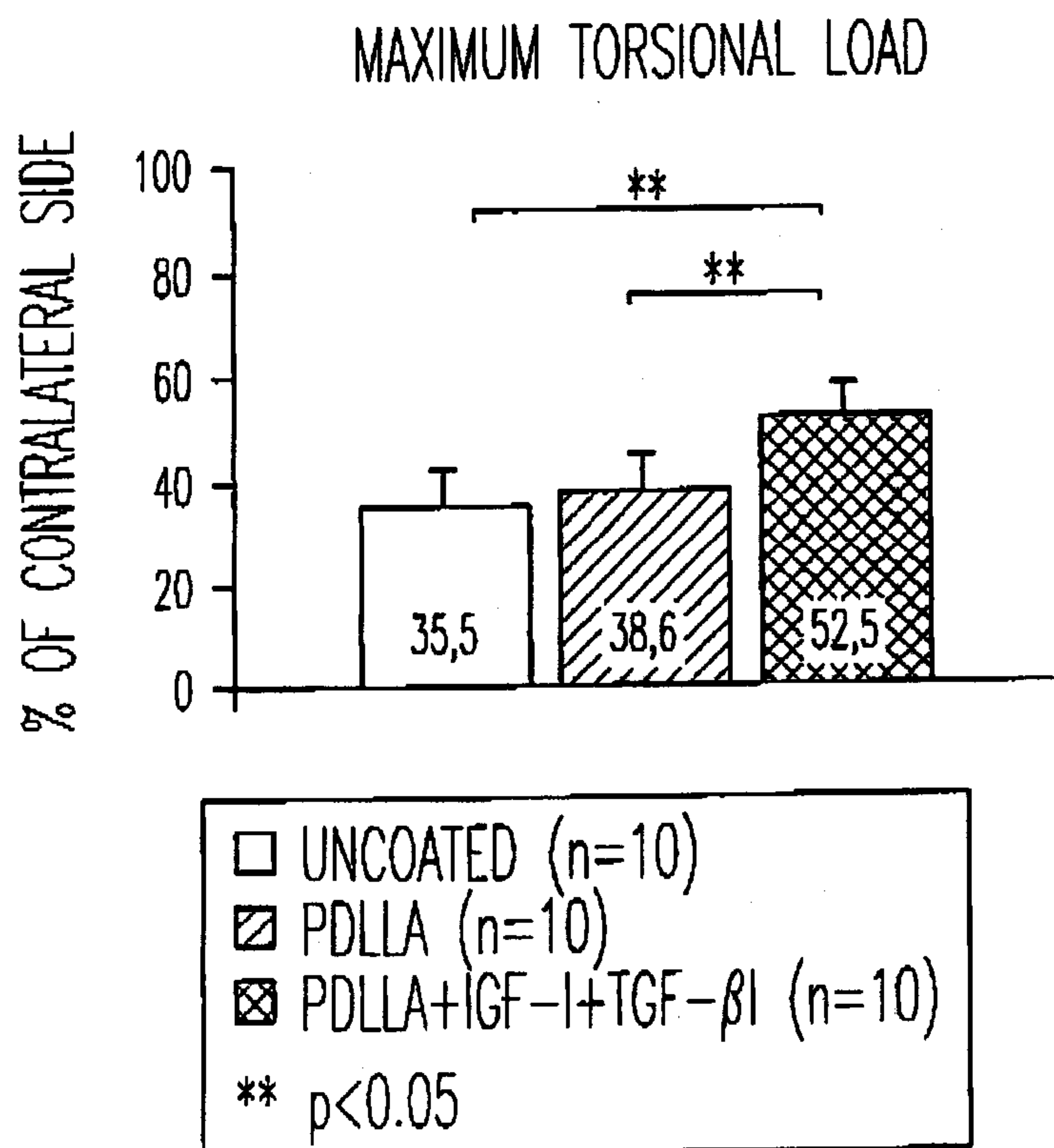
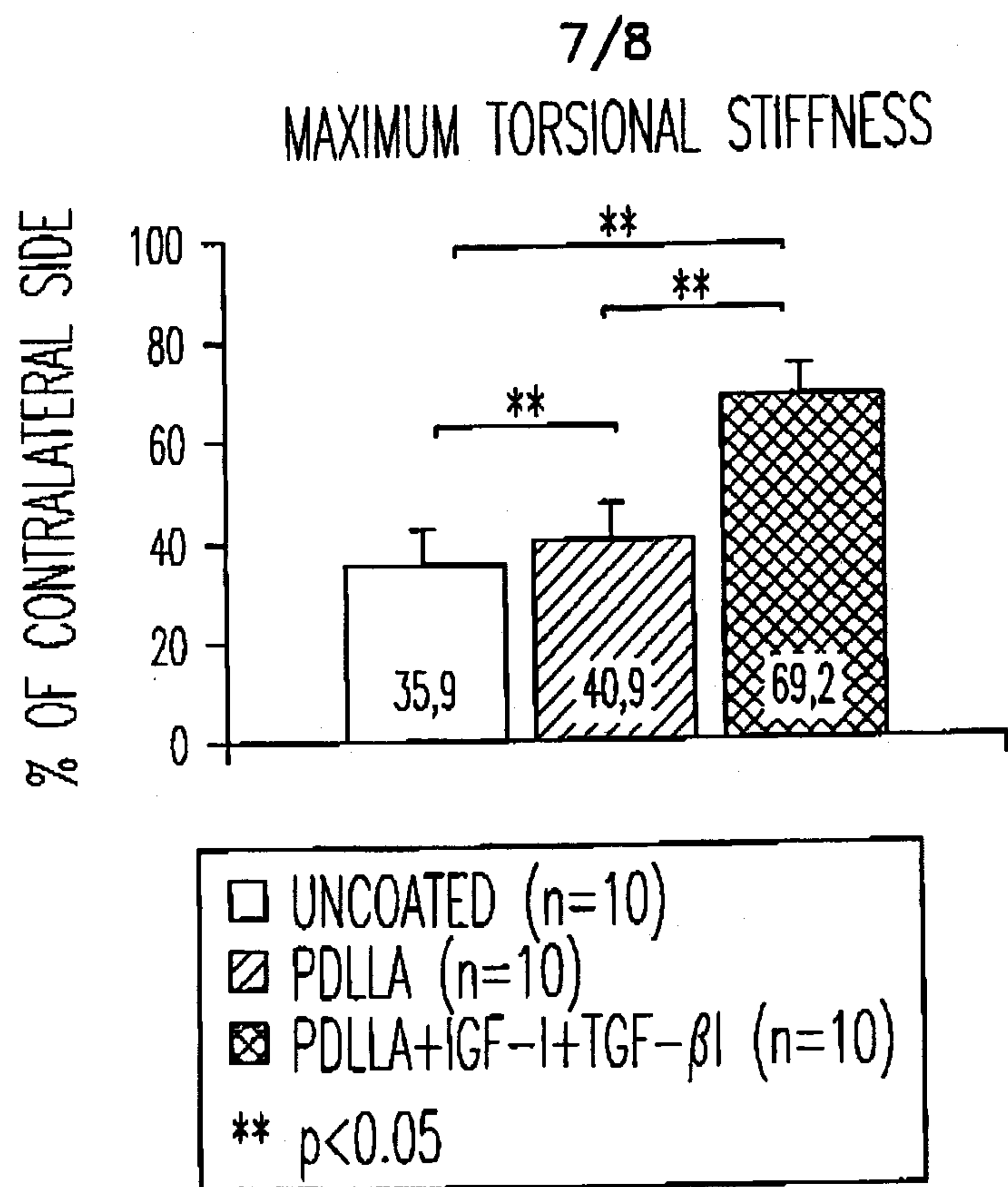
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CALLUS DENSITY AFTER 4 WEEKS



CARTILAGE PER CALLUS AFTER 4 WEEKS

*Fig. 5*

*Fig. 8*

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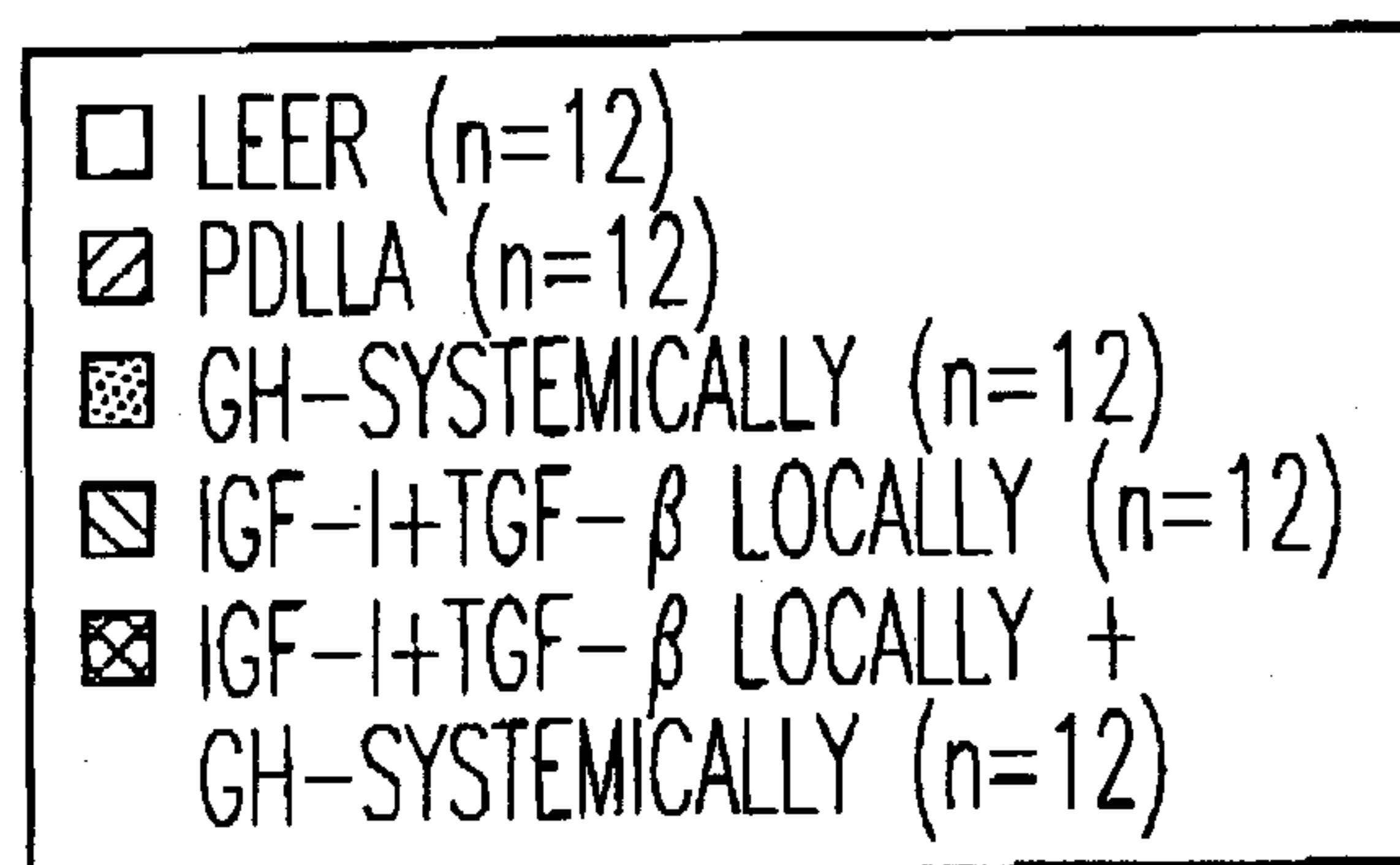
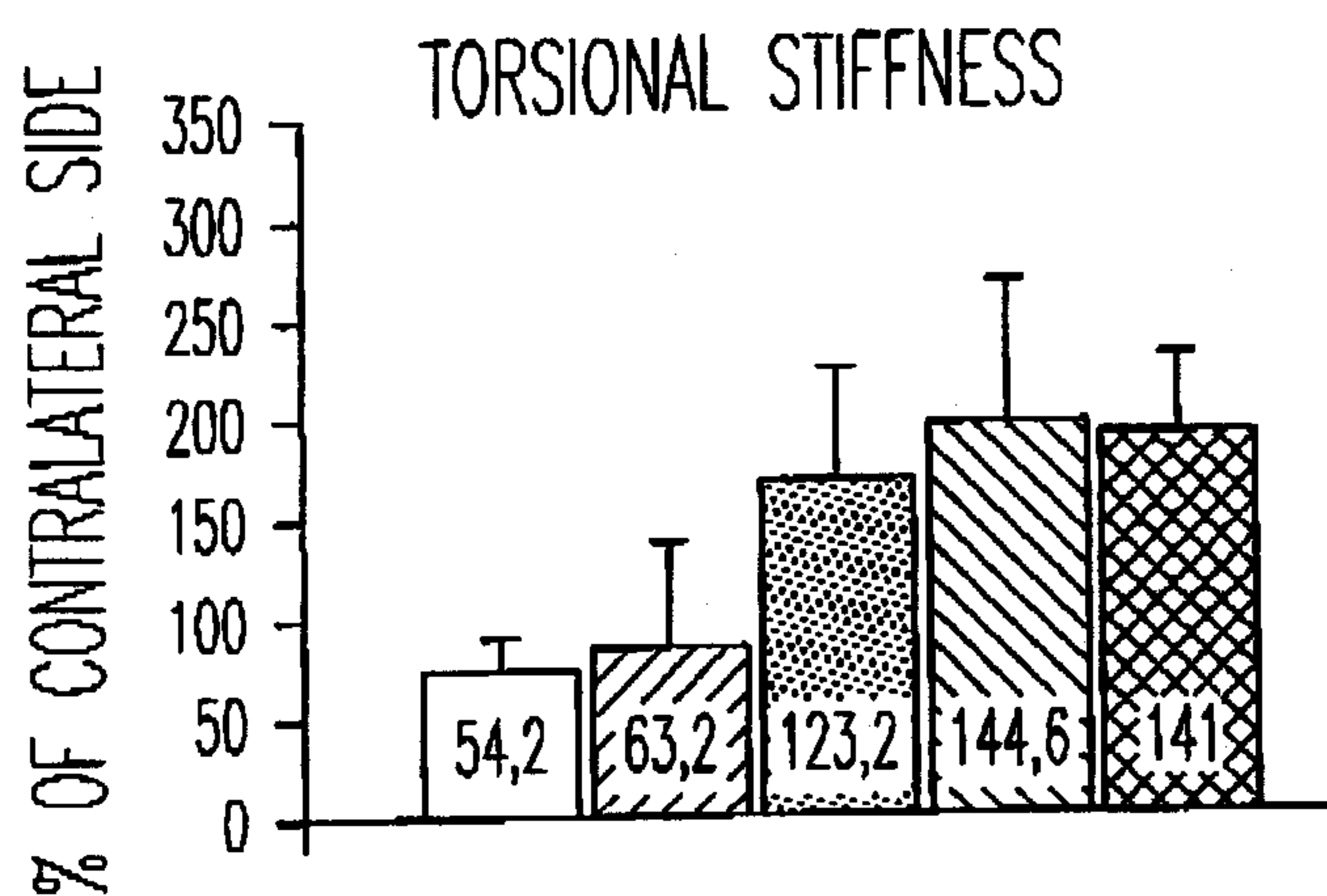
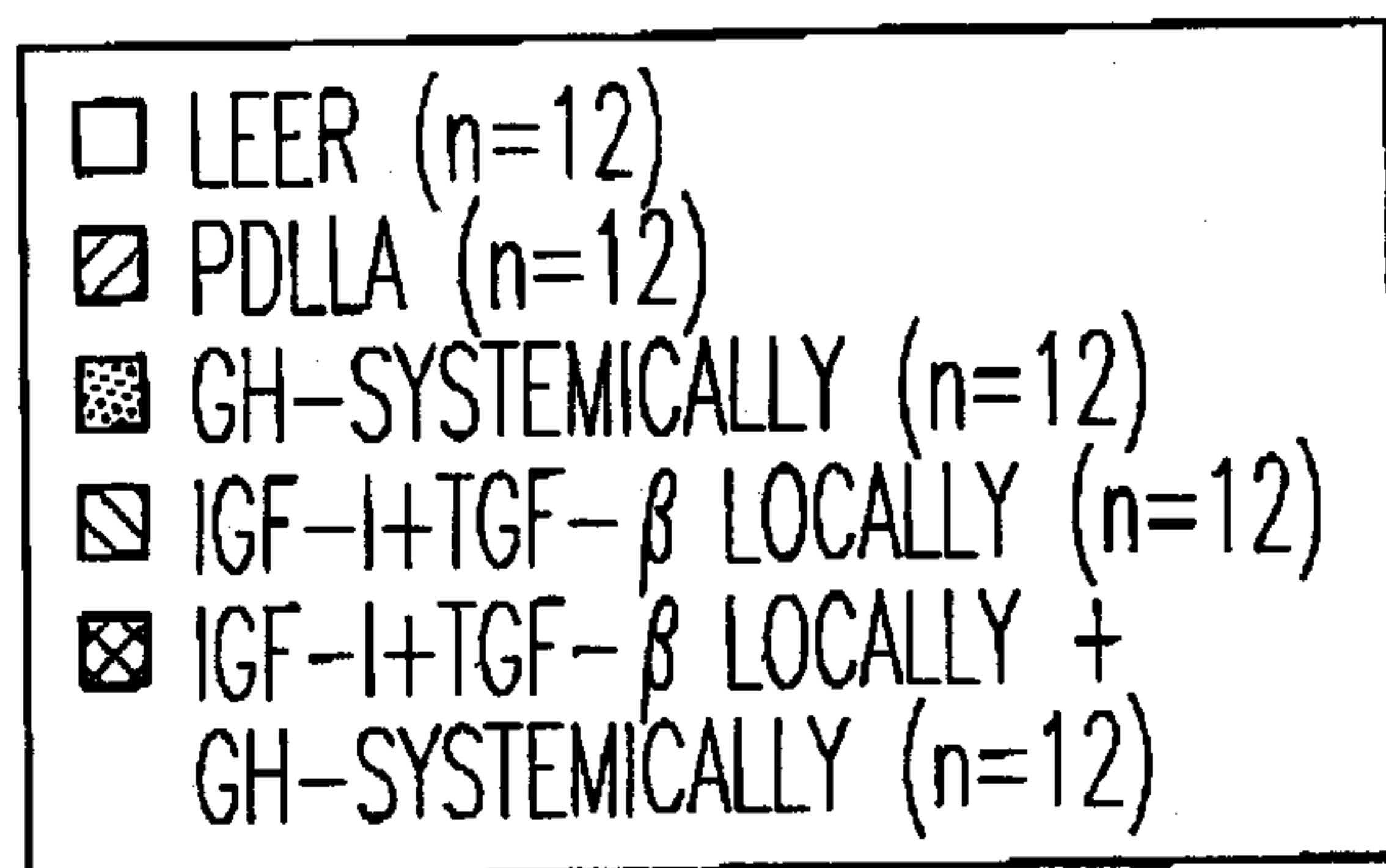
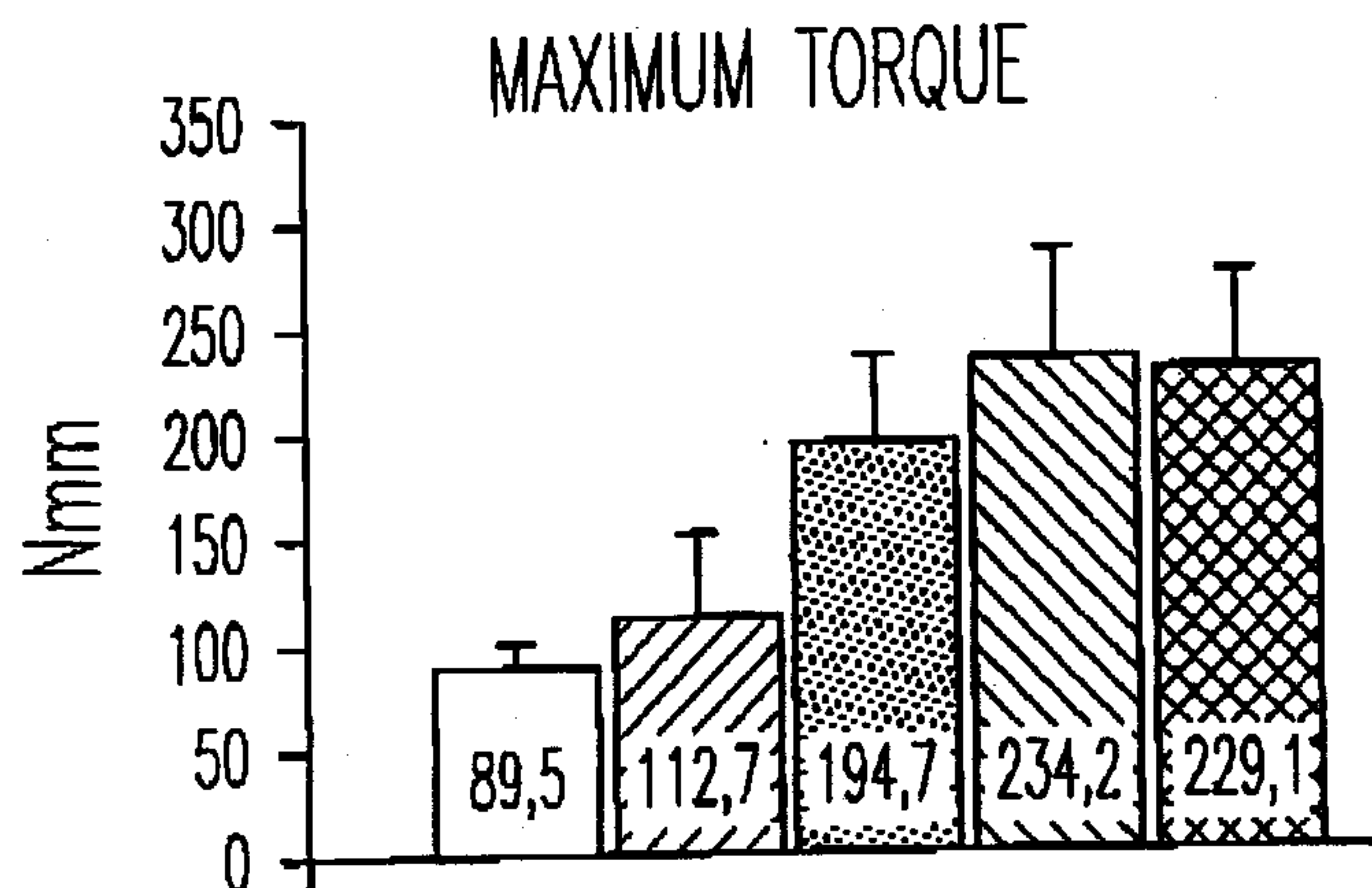


Fig. 9