



Original article

Pirfenidone vs Sodium Hyaluronate/carboxymethyl cellulose as Prevention of the Formation of Intra-abdominal Adhesions After Colonic Surgery. A Randomized Study in an Experimental Model[☆]



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A B S T R A C T

Introduction: Up to 93% of patients undergoing abdominal surgery will develop intra-abdominal adhesions with the subsequent morbidity that they represent. Various substances have been tested for the prevention of adhesions with controversial results; the aim of our study is to compare the capability of pirfenidone in adhesion prevention against sodium hyaluronate/carboxymethylcellulose.

Methods: A randomized, prospective, longitudinal experimental study with Wistar rats. They were divided into 3 groups. The subjects underwent an exploratory laparotomy and they had a 4 cm² cecal abrasion. The first group received saline on the cecal abrasion, and groups 2 and 3 received pirfenidone and sodium hyaluronate/carboxymethylcellulose respectively. All rats were sacrificed on the 21st day after surgery and the presence of adhesions was evaluated with the modified Granat scale. Simple frequency, central tendency and dispersion measures were recorded. For the statistical analysis we used Fisher's test.

Results: To evaluate adhesions we used the Granat's modified scale. The control group had a median adhesion formation of 3 (range 0–4). The pirfenidone group had 1.5 (range 0–3), and the sodium hyaluronate/carboxymethylcellulose group had 0 (range 0–1). There was a statistically significant difference to favour sodium hyaluronate/carboxymethylcellulose against saline and pirfenidone ($P < .009$ and $P < .022$ respectively).

Conclusions: The use of sodium hyaluronate/carboxymethylcellulose is effective for the prevention of intra-abdominal adhesions. More experimental studies are needed in search for the optimal adhesion prevention drug.

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Pirfenidona frente a hialuronato de sodio/carboximetilcelulosa como preventivos de la formación de adherencias intraabdominales tras cirugía colónica. Estudio aleatorizado en modelo experimental

RESUMEN

Palabras clave:

Adherencias
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Introducción: Hasta el 93% de los pacientes sometidos a una cirugía abdominal desarrollarán adherencias intraabdominales, con la subsecuente morbilidad que estas representan. Se han estudiado diversas sustancias para la prevención de adherencias con resultados controvertidos. El objetivo de nuestro estudio es comparar la capacidad de prevención de adherencias de la pirfenidona frente al hialuronato de sodio con carboximetilcelulosa.

Método: Estudio aleatorizado, prospectivo, longitudinal en modelo experimental en ratas Wistar. Se dividieron aleatoriamente en 3 grupos de estudio. A todos los animales se les realizó una laparotomía exploradora y se les provocó un deserosamiento de 4 cm² en el colon. El primer grupo recibió solución salina en la zona lesionada, los grupos 2 y 3 recibieron pirfenidona y hialuronato de sodio/carboximetilcelulosa, respectivamente. Al día 21 se sacrificaron las ratas y se evaluó la presencia de adherencias según la escala modificada de Granat. Registramos medidas de tendencia central y dispersión. Para el análisis estadístico se utilizó la prueba de Mann-Whitney.

Resultados: En grupo control, la mediana de formación de adherencias fue de 3 (rango 0-4), para el grupo pirfenidona fue 1,5 (rango 0-3) y para el grupo hialuronato de sodio/carboximetilcelulosa 0 (rango 0-1). El empleo de hialuronato de sodio/carboximetilcelulosa es estadísticamente superior en la prevención de adherencias comparado con la solución salina y con pirfenidona respectivamente ($p < 0,009$ y $p < 0,22$).

Conclusiones: El empleo de hialuronato de sodio/carboximetilcelulosa es efectivo para la prevención de adherencias intraabdominales. Son necesarios más estudios experimentales en búsqueda del fármaco ideal para la prevención de adherencias.

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Introduction

Abdominal and pelvic surgical operations represent the majority of elective and emergency surgical procedures. As a result of these, up to 93% of postoperative patients develop some type of intra-abdominal adhesions.^{1,2}

The clinical outcomes of these adhesions include infertility, pelvic pain, difficulty in subsequent abdominal surgery and intestinal obstruction. Colorectal surgery has been said to be the main cause of adhesions which lead to intestinal obstruction.^{3,4}

Depending on the series, up to 75% of patients will develop symptoms of intestinal obstruction, while 3.8% will require surgical treatment. Postoperative adhesions cause 20% of all cases of infertility, and 40% of cases of pelvic pain in women.³⁻⁵

There are few studies on the new methods for regulating the inflammatory response in the peritoneal cavity.⁶⁻⁸ Experimental studies have confirmed the importance of tumour necrosis factor alpha (TNF- α), transforming growth factor beta (TGF- β), interleukin 1 beta (IL-1 β) and interleukin 6 (IL-6), in the formation and maturation of intra-abdominal adhesions. All of these cytokines modulate the fibrinogenesis route and, as a result of this, by the end of the first week there are mature adhesions in the peritoneal cavity.⁹⁻¹⁶

The methods described in the literature to prevent intra-abdominal adhesions include types of surgical technique,

pharmacological, biological and physical methods, amongst others, with highly variable results. Products derived from carboxymethyl cellulose plus sodium hyaluronate are the ones which have been shown to give the best results, and they have even been approved now for use in human beings.^{6,17-20}

There is a type of salt in the market that is known for its antifibrotic, anti-inflammatory and antioxidant powers: pirfenidone. Although little is known about its mechanism of action, it is known to reduce the production of the cytokines involved in the formation of adhesions. This was proven by Tietze and Oku et al. in 2 different studies in animal models, as it reduces the expression of cytokines TNF- α , TGF- β , IL-1 and IL-6.^{21,22} In 1999 Iyer et al. documented the reduction in the expression of the procollagen gene in a pulmonary fibrosis model induced by bleomycin, reducing the formation of extracellular matrix.²³ As well as experimental models in pulmonary fibrosis, its efficacy has also been studied in vivo in renal, hepatic and cardiac fibrosis models, in which a reduction in the expression of TGF- β was observed.^{24,25}

Pirfenidone has also been shown to be safe in humans by prospective randomized studies. In 2007 Shi et al. studied the pharmacokinetic characteristics of pirfenidone in healthy patients. They found suitable absorption rates, with minimum adverse events that were tolerated well, and these events were reduced even more if it was taken with food.²⁶ In 2011 Carter reported the preliminary findings of 2 double-blind prospective randomized studies in patients with mild to

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