

Результаты клинического исследования применения противоспаечного геля Оксиплекс для снижения риска возникновения болевого синдрома и сопутствующих неврологических симптомов после поясничной дискэктомии

Results of Oxiplex U.S. Clinical Trial, published in SPINE

Rhyne AL, et al (2012). Oxiplex reduces leg pain, back pain and associated symptoms following lumbar discectomy. *Spine* 37:631-641

BACKGROUND

DESCRIPTION

Oxiplex® (also known as MediShield™ and Oxiplex®/SP Gel) is a flowable gel. The gel is a sterile, absorbable isotonic combination of polyethylene oxide (PEO) and sodium carboxymethylcellulose (CMC) with calcium chloride and sodium chloride in sterile water for injection. Oxiplex is non-pyrogenic.

INTENDED USE

Oxiplex gel is intended to be placed at sites of tissue injury in the epidural space following laminectomy, laminotomy, and/or discectomy to serve as a temporary mechanical barrier separating opposing tissue surfaces.

INDICATIONS

Oxiplex gel is intended to be used as an adjunct to posterior lumbar laminectomy, laminotomy, or discectomy procedures for reducing pain, radiculopathy, lower extremity weakness, and the incidence, extent, and severity of postoperative adhesions.

CLINICAL INVESTIGATION

The article published in Spine by A. Rhyne et al describes a very rigorous clinical trial that was carried out and monitored in 31 U.S. spine centers according to a set of rules approved by FDA.

This publication is a valuable and comprehensive source of information pertaining to Oxiplex's well-established characteristics, with regard to: EFFECTIVENESS – SAFETY – TOLERABILITY.

Summary

A U.S. multicenter, randomized, third-party blinded, controlled clinical trial to determine the safety and effectiveness of Oxiplex for the reduction of pain and symptoms following lumbar disc surgery was conducted. A total of 352 patients were randomized to receive surgery plus Oxiplex (Oxiplex group n=177) or surgery alone (Control group, n=175). The effectiveness of Oxiplex was evaluated by the Lumbar Spine Outcomes Questionnaire (LSOQ) and by physical evaluations to assess improvement in clinical outcome measures including leg pain, back pain and neurological symptoms.

Safety

There were no statistically significant differences in the number of subjects having serious adverse events (SAEs) or adverse events (AEs) or between the Oxiplex and Control groups. Serious adverse events related to the procedure or lumbar region in the treatment groups include cardiac disorders, gastrointestinal disorders, hepatobiliary disorders, cellulitis, pneumonia, wound infection, cerebral spinal fluid leakage, dural tear, hip fracture, incision site complication, nerve injury, wound secretions, musculoskeletal and

connective tissue disorders, headache, migraine, syncope, psychiatric disorders, asthma, pulmonary embolism, cholecystectomy, spinal fusion surgery and deep vein thrombosis. Adverse events related to surgery include constipation, nausea, vomiting, chills, pyrexia, incision site complication, pain, vertebral disc protrusion, weakness, stiffness, myalgia, dizziness, headache, hypoesthesia, hyporeflexia, sensory loss, insomnia and puritis,

One (1) reoperation occurred in the Oxiplex group, while six (6) reoperations occurred in the Control group by 3 months (Fisher's Exact test $P=0.0665$).

Postmarket surveillance of approximately 300,000 distributed devices intended for use following posterior lumbar spine surgery has resulted in no reports of adverse events that were attributable to the device.

Effectiveness

For each subject and for each follow-up evaluation period, measures were derived from the subjects' responses to the LSOQ: two pain severity measures (leg and back), leg weakness, physical symptoms, subject satisfaction, disability days, and activities of daily living. All subjects were treated surgically and showed substantial improvement as a result of surgery.

The primary effectiveness outcome of improvement in leg pain at 1 month, 3 months and 6 months showed a statistically significant interaction between treatment and baseline back pain in the Intent-to-Treat (ITT) population ($P=0.0113$). Subjects with severe back pain at baseline showed significantly greater improvement (reduction from baseline) in leg pain in the Oxiplex group compared to subjects in the Control group. The most prominent gain in improvement in leg pain from baseline by Oxiplex subjects was observed at the 6-month visit ($P=0.0507$). Subjects with severe back pain at baseline showed greater improvement ($P=0.0193$).

At 6 months, Oxiplex subjects with severe baseline back pain had significantly higher satisfaction scores ($P=0.0456$). Additional subgroup analyses demonstrated improvements across all subjects for each of the effectiveness measures: leg pain, back pain, leg weakness, physical symptoms, satisfaction, disability days, and activities of daily living. The mean improvement was higher for Oxiplex subjects than for Control subjects for all seven endpoints ($P=0.008$).

ASSUMPTIONS:

- Study protocol was approved by FDA
- The study itself was carefully monitored according to FDA requirements throughout its execution.
- Very accurate clinical evaluation was applied in the recruitment process of the two groups of Patients (i.e., $N=177$ treated + $N=175$ control), as well as in the follow-up process.
- The Lumbar Spine Outcomes Questionnaire (**LSOQ**) that was developed at Johns Hopkins University was used for pre-operative assessment and post-surgical follow-up, as it is recognized as being a convenient quality of life instrument, based not only on pain evaluation but on a complex array of parameters pertaining to performance of common activities of daily living .
- Renowned and experienced surgeons.

DISCUSSION SUMMARY

- EFFECTIVENESS DEMONSTRATED IN TERMS OF:

1. Significant *pain reduction*, throughout a 6- month follow-up period, PARTICULARLY in patients with severe back pain at baseline (pre-operative) measurement.
2. Significantly fewer *re-operations* in the Treatment Group (only 1), compared to the Control Group (6).
3. Lower number of *disability days* recorded in the Treatment Group, compared to the Control Group.
4. Lower incidence of *musculo-skeletal* abnormalities, and *sensory deficits* recognized in the Treatment Group, versus the Control Group.

- SAFETY DEMONSTRATED IN TERMS OF:

1. No CSF leaks recorded in the Treatment Group.
2. No post-op inflammatory-syndrome occurrence in the Treatment Group.
3. Assessment of Adverse Events performed concurrently at 1 – 3 – 6 months post-op; no significant differences between the Treatment and Control groups.

- TOLERABILITY DEMONSTRATED IN TERMS OF:

1. No resorption-related unexpected and/or undesired side-effects recorded in the Treatment Group, in the immediate post-op, as well as throughout the 6- month follow-up period.

REMARKS

- The “LSOQ” is a simple and effective tool that is useful in quantifying not only leg pain and back pain scores, but also in evaluating post-surgical outcomes in patients with lumbar spine disorders.
- OXIPLEX/MEDISHIELD acts as a physical barrier that separates adjacent tissues. This mechanism of action reduces exposure of sensory nerves to biochemical and cellular pain mediators, generally regarded as “neurotoxins” (cytokines, etc.), which initiate the biochemical “cascade” generating fibrous tissue formation that can lead to adhesions. Adhesions, in turn, can encapsulate and compress the neural structures, often leading to FBSS.

CONCLUSION

- OXIPLEX has been shown to be a safe and effective device to be placed around neural tissues following spine surgery to reduce the formation of adhesions and related symptoms such as pain.

- NOTES*

CONTRAINDICATIONS

Contraindicated for use in the presence of frank infection.

WARNINGS

Do not inject Oxiplex into blood vessels or allow it to enter blood vessels.

PRECAUTIONS

For professional use only.

Use Oxiplex according to the instructions for use. Oxiplex is supplied sterile and is for single use only. Do not use if the package is damaged or opened. Do not resterilize. Discard any opened or unused product. Safety and efficacy of Oxiplex have not been studied under conditions of reuse of device and/or applicator. Reuse may lead to immunological response and/or infection due to cross contamination, improper storage and/or handling.

Oxiplex is not a dural sealant. Any dural defects should be repaired prior to use.

The use of Oxiplex in combination with pharmaceuticals, biologics, other adhesion prevention products or other medical devices has not been evaluated.

Oxiplex has not been evaluated in the presence of a malignancy in the spine.

Oxiplex has not been studied in the presence of hemostatic agents.

Oxiplex has not been studied at the site of bone fusion.

Oxiplex has not been studied in the presence of surgical drains.

The use of Oxiplex has not been evaluated in children, or during pregnancy.

Preclinical reproductive toxicity studies have demonstrated the safety of Oxiplex in animals. No clinical studies have been conducted in women who have become pregnant in the first month after application of Oxiplex. Therefore, avoiding pregnancy during the first complete menstrual cycle after application of Oxiplex should be considered. The use of Oxiplex in nursing mothers should be avoided.

Foreign body reaction may occur as with any surgical adjuvant.

After use, Oxiplex may be a potential biohazard. Handle and dispose of Oxiplex in accordance with accepted medical practice and applicable national, local and institutional requirements.

SIDE EFFECTS

There are no known side effects associated with the use of Oxiplex in humans.

ADVERSE REACTIONS

General

Adverse events associated with surgery include: fever (within 36 hours postop), chills, pain, redness, swelling, itching, bleeding, bruising, hemorrhage, hematoma, seroma, wound secretions/drainage, cellulitis, weakness, stiffness, spasms, and tightness at the surgical site, and death.

Spine Surgery

In addition, adverse events associated with spine surgery include: atelectasis/pneumonia, adjacent level disease, arachnoiditis, cavernous malformation, deep vein thrombosis, pulmonary embolism, dural tear, spinal fluid leak, fibrosis, facet fracture, wound infection, myocardial infarction, nerve injury, vascular injury, delayed union/non-union of fusion, spinal cord injury, paresis, myelopathy, including paralysis, additional surgery, failure of the surgical procedure to improve symptoms and/or function.

Adverse events associated with cervical spine surgery also include: bone graft movement/graft dislodgement, cervical soft-tissue swelling, dysphagia, esophageal injury, axial neck pain, hardware failure, Horner's syndrome, instability, kyphosis, pseudoarthrosis, stroke, trachea injury, upper airway obstruction, respiratory failure, and neurologic deficit.

Adverse events associated with thoracic spine surgery also include: intercostal neuralgia (thoroscopic procedure).

Adverse events related to lumbar spine surgery also include: cardiac disorders, visceral injury, gastrointestinal disorders, hepatobiliary disorders, cellulitis, hip fracture, incision site complication, musculoskeletal and connective tissue disorders, headache, migraine, syncope, psychiatric disorders, asthma, cholecystectomy, ileus, constipation, nausea, vomiting, chills, pyrexia, incision site complication, procedural pain, arthralgia, back pain, intervertebral disc protrusion, myalgia, pain in extremity, dizziness, headache, hypoesthesia, hyporeflexia, sensory loss, insomnia and puritis.

* See the Instructions for Use for more information.

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