DMSO: Applications in Plastic Surgery

The authors point out that dimethyl sulfoxide (DMSO) increases tissue perfusion and may effectively treat or prevent ischemia in flaps. They recommend application of topical DMSO every 4 to 6 hours, until blood flow improves, to areas that show signs of ischemia or less than adequate perfusion. Other potential cosmetic surgery uses of DMSO include areas of skin care, pain relief, and treatment of keloids. (Aesthetic Surg J 2005;25:201-209.)

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dimethyl sulfoxide [(CH₃)₂SO] (DMSO) is an organic solvent of which plastic surgeons should be aware, primarily because its ability to increase perfusion has led to its use in decreasing ischemia in tissue flaps. We have personally had success using topical DMSO to improve skin perfusion following abdominoplasty and face lift procedures, and would definitely consider using DMSO in conjunction with other procedures that pose a risk for ischemia.

DMSO has multiple applications in medicine and industry and is readily available throughout the United States on Web sites and in health food stores. However, there has been a lack of development in the potential medical applications of DMSO. No single pharmaceutical company was able to get an exclusive patent for DMSO; therefore, the pharmaceutical industry has not assumed the expense of studying DMSO beyond its uses as a drug component. Further, DMSO has so many possibilities that it does not easily fit into a drug category. Aspirin would have encountered similar hurdles if it were not widely available a century ago. Despite the controversy that has surrounded DMSO for nearly 40 years, it seems to have a wide safety margin, especially for the topical applications most useful to plastic surgeons.

Herein we will discuss the potential uses of this substance in plastic surgery and then provide background information on chemical composition, FDA history, toxicity, relationship to tissue and flap perfusion, and other medical applications.

DMSO was first synthesized in 1866 as a colorless organic solvent derived from byproducts of wood and paper pulp industries. In 1961, nearly a century after its synthesis, investigations into possible medical applications of DMSO began when Dr. Stanley Jacob, then head of the organ transplant program at Oregon Health Sciences University, was looking for substances that might be effective as organ preservatives.¹ Jacob noticed that DMSO rapidly, but harmlessly, penetrated deep into his skin. Since that discovery, more than 12,300 English-language articles about the medical implications of DMSO and its clinical mechanisms of action have been cataloged by the National Library of Medicine. Further, thousands of in vitro and in vivo laboratory studies have been conducted,¹ and millions of patients around the world have been treated with various forms of DMSO, referred to by chemists as Me₂SO.

In 125 countries, including Canada, Great Britain, Germany, and Japan, DMSO is available in a variety of concentrations for topical, injectable, and intravenous uses. It is prescribed for medical conditions such as scleroderma, rheumatoid- and osteoarthritis, ulcerative colitis, and head injuries.

**DMSO and Flap Perfusion in Plastic Surgery**

In 1968, McFarlane et al² reported on the use of DMSO to prevent necrosis in experimental pedicle flaps; numerous studies that followed confirmed this discovery.³-⁶ The mechanism of action is not fully understood, but DMSO is known to stimulate histamine release,⁷,⁸ and histamine release triggers vasodilation.

Both topical and intravenous DMSO solutions have been studied in animal models of pedicle, island, and cutaneous flaps. One study of abdominal island flaps in
rats compared control animals that received saline injections with rats injected with intraperitoneal DMSO. Flaps in the treatment group showed significantly increased blood perfusion by postoperative day 3 as measured by laser Doppler velocimetry and perfusion fluorometry.4

In another controlled rat study, 9 × 4-cm pedicle flaps were elevated on the abdomen. The epigastric vein was occluded with a clamp for 8 hours before the clamp was removed and the flap resutured to its bed.3 Two groups of animals received intraperitoneal saline. Three groups received intraperitoneal DMSO at different timepoints: (1) at reperfusion only; (2) at reperfusion and then every day for 5 days; or (3) before surgery, at reperfusion, and for 5 days after surgery. The area of flap survival was measured with a sonic digitizer. When administered as a single dose at reperfusion, DMSO did not increase flap survival compared with controls receiving saline. However, both groups receiving DMSO at reperfusion and for 5 postoperative days had a significantly greater percentage of flap survival area: 78% to 86% for DMSO versus 32% to 34% for saline (P < 0.01).

The survival of skin flaps with topically applied DMSO was also investigated. In this model, 10 × 2.5-cm flaps were elevated and then resutured on the backs of rabbits.6 Four groups were compared: (1) those treated with saline; (2) those treated with 8% hydrogen peroxide (H2O2); (3) those treated with 50% DMSO; and (4) those treated with 50% DMSO + 8% H2O2. DMSO with H2O2 was studied because H2O2 stimulates the release of oxygen when applied to tissues, and DMSO penetrates cell membranes; so, theoretically, DMSO could deliver hydrogen peroxide throughout the flap. Treatments were topically administered 3 times daily for 7 days, beginning immediately after surgery. Transcutaneous oxygen tension (PtcO2) in the flaps was measured 72 hours after surgery, and the percentage of surviving skin area was measured by planimetry 7 days after flap elevation.

There were no significant differences in area of flap survival for the groups that received saline (71% survival), 8% H2O2 (72% survival), or 50% DMSO (76% survival). However, flaps that received the combination of DMSO + H2O2 had a significantly larger area of survival (92%). The mean PtcO2 value also was significantly different for the DMSO + H2O2 group (95% versus 74% for the other 3 groups).

Reported clinical studies of DMSO and flap survival have thus far been limited to mastectomy patients. Rand-Luby et al10 performed a randomized, prospective study of skin flap viability in patients undergoing mastectomy and inguinal lymphadenectomy. Twenty-four patients treated with 60% DMSO topically applied to their flaps every 4 hours for 10 days after surgery were compared with 27 patients who had surgery alone. The maximum area of flap ischemia was traced by a masked observer and measured by cut and weigh technique. The mean area of ischemia for the DMSO-treated group was 16.3 U versus 44.9 U for the controls (P = 0.01).

Tissue expansion in patients undergoing immediate breast reconstruction following modified radical mastectomy was studied by Raposo and Santi11 to determine whether DMSO could reduce expander pressure and length of treatment. One group of 20 patients underwent standard tissue expansion, and in another group of 20 patients, 60% DMSO-soaked surgical sponges were left on the skin overlying the expander for 30 minutes prior to expansion. A statistically significant difference in the number of weekly expander filling sessions was found, with a mean of 6 sessions for the untreated group and a mean of 4 sessions for the DMSO-treated group. In addition, there was a significant difference in the average inflated volume per session; the untreated group had an average of 90 mL added to their expanders per session, compared with the DMSO-treated group who had an average of 120 mL added to their expanders per session. The ability to complete tissue expansion more quickly following mastectomy can be considered a real benefit for these patients.

Vinnik5 has reported that he achieves maximal tissue expansion in minutes by applying topical DMSO, which permits immediate placement of large permanent implants after mastectomy. He also uses topical DMSO to maximize the area of skin resection in patients undergoing abdominoplasty, thereby maintaining good flap perfusion.

We have observed skin perfusion improvement with topical application of DMSO following abdominoplasty and face lift procedures. Figure 1 demonstrates the immediate and obvious impact of DMSO on skin perfusion in a woman undergoing abdominoplasty. We would like to emphasize, however, that we do not recommend using DMSO as a way to increase the area of resection during surgery. DMSO should be used to increase perfusion. Resection should always be kept within safe margins.

It seems reasonable to try DMSO when other more traditional methods of improving circulation, such as releasing tension, relieving kinks from pedicles, or...
decreasing pressure, have failed. If an area shows signs of ischemia or appears to have inadequate perfusion, application of topical DMSO, every 4 to 6 hours until blood flow improves, should be beneficial. The product is inexpensive and easy for patients to use at home. Although DMSO probably cannot repair areas of necrosis, it may prevent loss of circulation in ischemic tissues or decrease the size of a possibly necrotic area.

Experimental studies have found DMSO to be effective in tissue ischemia related to either arterial or venous obstruction. Consequently, the cause of ischemia should not be a consideration when contemplating DMSO treatment.

Concentrations of topically applied DMSO in the flap studies cited vary from 50% and 60% to our use of 99%. The literature review indicates that the ability of DMSO to cross all membranes varies according to DMSO strength. The most effective DMSO strength for penetrating skin is a solution between 70% and 90%. For reasons unknown, concentrations higher than 90% are less effective. Our choice of DMSO concentration will be less than 90% in the future. Much lower concentrations of DMSO—in the range of 1% to 8%—are sufficient for crossing membranes other than skin.

The 60% DMSO concentration used in the context of tissue expansion following mastectomy may have been chosen because lower concentrations can minimize skin reactions, which could be especially important when the skin above an expander is soaked in DMSO for 30 minutes. (Even a 60% DMSO concentration produced impressive results in these studies.) In our experience, topical use of DMSO has been limited to a few days at most, and no skin irritation has been seen. Any erythema or wheal that did occur should disappear soon after DMSO treatments are stopped.

**Other Possible DMSO Applications in Plastic Surgery**

**Keloids.** Biopsies of keloids have shown histologic improvement after DMSO treatment. Thus, DMSO may be effective for this difficult problem.

**Pain relief.** Several animal studies have explored the analgesic action of DMSO, which seems to block peripheral nerve C fibers. One study found that DMSO was not only as effective as morphine for pain relief, but that its effect persisted several hours longer than that of morphine. DMSO also has been used around the world for decades as a topical analgesic for treatment of arthritis pain. The analgesic property of DMSO combined with its ability to rapidly deliver drugs into tissues may be applicable to topical lidocaine. Some studies have determined that transdermal delivery of lidocaine is enhanced when DMSO is applied first. The pain suppression effect of lidocaine when dissolved in 0.1% DMSO solution was markedly potentiated in another study.

A most intriguing investigation involved topical anesthesia in patients with vascular malformations who underwent typically painful pulsed dye laser treatments. Mallory et al mixed a 25% lidocaine base in 70% DMSO for topical application prior to laser treatments. Although this mixture did not produce total anesthesia, it was sufficient to allow patients to complete treatment with minimal discomfort rather than return several times for additional laser therapy. An in vitro permeation experiment found that lidocaine plus DMSO achieved significantly greater permeation of skin than did acid mantle cream or EMLA (AstraZeneca, Waltham, MA). Furthermore, no patient experienced stinging or itching at the lidocaine/DMSO application site, though there was transient mild erythema.
To avoid toxicity, limits to amounts of topical lidocaine need to be established, but the preparation used by Mallory et al included no more than 6 drops of 25% lidocaine, which is far less than the amount of drug delivered by injection.

If, with the addition of DMSO, topical lidocaine could be delivered into the skin more quickly, or if lower doses of lidocaine could be used, patients would greatly benefit. For example, patients would not have to wait as long before receiving painful injections, including tissue fillers, and suturing could be completed more quickly, and without lidocaine injection. This would be especially helpful for treating children. DMSO can carry nonionized molecules through skin if their molecular weight is less than 3000. The molecular weight of lidocaine is 234.

**Skin care applications.** Using various dyes as visual tracers, followed by biopsies, a study of DMSO penetration into human skin demonstrated that the stratum corneum was completely stained. Thus, DMSO penetrated rapidly and deeply into the horny layer. This suggests that DMSO may increase the penetration of some facial peel chemicals down to the stratum corneum.

Antioxidants, such as vitamin C, are important components of good skin care. DMSO is perhaps the most powerful free radical scavenger—at least against hydroxyl—and a well tested carrier of other substances. Therefore, DMSO may have a role in skin rejuvenation. DMSO also inhibits bacteria growth, including *Staphylococcus aureus*, so it may be of benefit in treating acne.

An unfortunate side effect of DMSO used in any form (intravenous, injected, or topical) is that it causes a garlic-like breath odor that is not only unpleasant but also poses an “alert” that makes it difficult to conduct DMSO blinded clinical trials. Also, skin care products that caused a garlic-like breath odor would be a challenge to market.

DMSO is metabolized in humans by oxidation into dimethyl sulfone (MSM), or by reduction into dimethyl sulfide (DMS), both of which are excreted in urine and feces. DMS is eliminated through the breath and skin and is the metabolite responsible for the garlic odor of DMSO. Newer forms of DMSO, such as MSM, which is also known as DMSO2, are available that do not produce this odor, but they lack scientific testing. Dr. Stanley Jacob, considered the father of DMSO research, markets MSM and oral DMSO on his Web site (www.jacoblab.com) as a nutritional sulfur supplement ingested in liquid or crystal form. MSM or DMSO2 is probably also available in health food stores. Other Web sites sell MSM in capsule or powder form. These products apparently can be added to liquids for ingestion or mixed with distilled or deionized water or lotion for topical application. We do not know how the actions of these available MSM products compare with DMSO, but these products deserve further investigation if they do eliminate the garlic odor.

**DMSO and Free Radicals**

DMSO is a small polar molecule (78 m.w.) with sulfur in the center, 2 methyl groups, and an oxygen atom at the apices. The oxygen atoms carry a nonbinding electron pair. Its structure makes DMSO soluble in aqueous and organic media, and DMSO has become one of the most common solvents for the in vivo administration of water-insoluble substances. In fact, it is the only solvent that can effectively dissolve some hydrophobic drugs.

Because of its small size and structure, DMSO molecules readily cross the membranes of skin, cells, and organelles. Furthermore, DMSO molecules can associate with a wide range of constituents, including water, proteins, carbohydrates, nucleic acid, and ionic substances. Radioactive tracer studies of DMSO absorption in humans found that 5 minutes after cutaneous application, DMSO is detectable in the blood; after 1 hour, it is detectable in the bones.

The free electron pairs of its oxygen atoms allow DMSO molecules to transfer electrons and accept hydrogen bonds. This structural characteristic makes DMSO a potent scavenger of free radicals, particularly hydroxyl (OH•), which is the most reactive free radical in biological systems. DMSO is such an effective scavenger because it is specific for OH• and can reach the sites of OH• generation, down to the mitochondrial level.

It is widely believed that the production of oxygen-derived free radicals is a major cause of ischemia and reperfusion injuries. The free radical scavenging ability of DMSO molecules also may figure prominently in the anti-inflammatory properties attributed to DMSO. The Table is a partial list of some medical applications of DMSO that have been published in peer-reviewed journals. A more complete list can be found in the articles by Santos et al and Jacob and Herschler.

**DMSO and the FDA**

The US Food and Drug Administration (FDA) halted all human studies of DMSO in 1965 when a woman in...
Ireland died of an allergic reaction after taking DMSO and several other drugs; however, her cause of death was never precisely determined. Also in 1965, pharmaceutical companies noted a refractive index change in the lenses of dogs, rabbits, and pigs treated with DMSO at doses 50 to 100 times higher than typical doses used in humans. The lenses were not opaque, and no microscopic or chemical differences were detected. The lens problem was not observed in any humans or other primates who at that time were experimentally treated with DMSO in the United States or elsewhere. However, since pretreatment eye examinations had not been performed in patients receiving DMSO, the absence of lens changes could not be confirmed. The lens trouble in lower mammals was sufficient evidence for the FDA to conclude that DMSO was highly toxic, and almost all United States-based research was stopped. Since 1965 the FDA has permitted very little work with DMSO.

However, the FDA has approved DMSO as a preservative for transplant organs and for symptomatic relief of interstitial cystitis through intravesical instillation. DMSO is also approved as a component of pharmaceuticals, and its properties as a drug “carrier” are well known. Molecular weight, shape, and electrochemistry determine which drugs DMSO can effectively carry through cell membranes. In addition to these human uses, the FDA has approved topically applied DMSO for the treatment of musculoskeletal disorders in horses and dogs, and it is widely used in horse racing stables as a pain-relieving liniment.

In 1978 the FDA approved the use of DMSO alone for treatment of interstitial cystitis and other inflammatory conditions of the genitourinary tract, such as radiation cystitis and chronic prostatitis. Typically, RIMSO-50, a 50% solution of DMSO (Edwards Lifesciences, Irvine, CA), is slowly instilled into the bladder with treatments repeated as frequently as needed to reduce symptoms. In one study, objective endoscopic improvement was seen in 85% of patients and 60% had an increase in bladder capacity.38 Because it lacks side effects, is inexpensive, and can be used in an office setting, intravesical DMSO is a treatment that may eliminate the need for surgery in many patients. It is believed that the anti-inflammatory and muscle relaxant properties of DMSO are responsible for the improvement in patients with interstitial cystitis.

A premarket approval application is currently before the FDA for the Onyx LES Liquid Embolic System (Micro Therapeutics, Inc., Irvine, CA), a device that incorporates DMSO for embolization of arteriovenous malformations in the brain. In this device, a mixture of ethylene vinyl alcohol copolymer and DMSO is delivered through a micro catheter to the target lesion and released to embolize the arteriovenous malformation. This Onyx system is currently used in Europe for intracranial aneurysms that cannot be treated with surgery or have not responded to other occlusion attempts.39 In this context, the FDA may be willing to approve the use of DMSO in a potentially life-saving device that requires minimal patient exposure.
DMSO and Toxicity

To address the FDA concern about lens changes in mammals and possible DMSO toxicity, a human study was undertaken in 1967-68. DMSO was administered to volunteers from a prison population in California who were involved in either a short-term (14 day) or long-term (90 day) study organized by Brobyn.40 A battery of tests were conducted before, during, and after the study start and stop points, including complete weekly physicals, ophthalmologic examinations, bone marrow studies, cerebrospinal fluid analysis, neurological exams (including electroencephalograms), pulmonary function studies, and electrocardiograph exams, as well as regular urine and blood analysis (including the full range of blood chemistries). The purpose of the tests was to look for hepatic, renal, or hematologic changes. The same examinations and testing regimen were administered to untreated controls at the same time intervals. In the experimental group, an 80% solution of DMSO gel was topically applied at 1 g/kg daily to 65 subjects for 14 days and to another 40 subjects for 90 days.

Data analysis revealed no significant differences among those receiving DMSO or the controls on any variable, with one exception: a small percentage of treated subjects had a slightly elevated peripheral eosinophil count. This eosinophilia was believed to result from the cutaneous histamine-releasing effect of DMSO. As expected, skin irritation (wheal and erythema with drying and scaling) was a common reaction to DMSO, but all reacting skin returned to normal within 3 weeks after treatment. No ocular or lens abnormalities occurred in the treated subjects.

Other investigations of lens abnormalities found no changes among patients with scleroderma treated with topical DMSO for 3 to 12 months.41,42 Nor did these studies find any other signs of possible systemic toxicity. The same was true in an investigation of rhesus monkeys given daily intravenous doses of 3 g/kg 40% DMSO for 9 consecutive days. The animals were examined during the following 4 months for changes in their eyes, blood chemistry, hematology, urine, and neurological and cardiovascular systems.43 After 4 months, the monkeys were sacrificed and received gross and microscopic pathological examinations. There were no significant differences between the monkeys that received DMSO compared with those that received intravenous saline.

Experiments have been performed to examine the toxicity and teratogenicity of various solvents used in medicine and pharmacology. In a study of frogs, DMSO was found to be the least toxic and least teratogenic solvent tested; formamide was the most toxic, and ethanol was the most teratogenic.44 Experiments exploring toxicity in mice have tested DMSO, polyethylene glycol 400 (PEG 400), dimethylformamide (DMF), absolute ethanol (EtOH), and benzyl alcohol (BeOH).45 There were no major differences in acute toxicity of the solvents in 3 mouse strains, although DMSO was less toxic in 1 strain, and BeOH and EtOH were less toxic in the other 2 strains.

The Brobyn prison study demonstrated that even though topical DMSO does not seem to be toxic when given at doses 3 to 30 times the typical human dose for up to 3 months, it is not without side effects. In addition to skin irritation, daily high-dose dermal application produced sedation and occasional insomnia or nausea in a small number of subjects. Even fewer men in the treated group reported dizziness or diarrhea.40 Intravenous administration of DMSO is more likely to produce adverse reactions, though they are uncommon; examples include red cell lysis with DMSO concentrations above 40%,46 and hypernatremia with fluid overload when DMSO concentrations were 10% or less.47 Allergic reactions are rarely reported.24

DMSO and Tissue Perfusion

Several different mechanisms may explain how DMSO counteracts ischemia after trauma. It is believed that DMSO protects the integrity of cell membranes during injury,48 especially defending against attack by hydroxyl radicals, which are generated at a high level after ischemic injury. This ability to preserve cell membranes may partially explain how DMSO improves cerebral and spinal cord blood flow after injury.49 In experimental cerebral ischemia, DMSO prevents or breaks up platelet aggregation,50 which may either promote ischemia or extend it. DMSO also has been found to prevent thrombus formation in vivo.

One of the more intriguing characteristics of DMSO is its potential to increase perfusion in injured tissues. Investigators have been studying this application of DMSO in cerebral ischemia since the 1970s.51-54 To examine DMSO in a clinical setting, 20 patients in Turkey with severe closed head injuries were given intravenous DMSO.55,56 In both studies (10 patients per study) DMSO rapidly reduced intracranial pressure, increased cerebral perfusion pressure and blood flow, and
improved outcomes so that most patients had no residual deficits.

Experimental studies of animals have found that, in addition to the brain and spinal cord, DMSO reduces the damage caused by ischemia in other organs. Intravenous DMSO was very effective in reversing acute ischemic renal failure in rats. DMSO increased myocardial perfusion in dogs and rats and has effectively improved liver perfusion after microvascular injury in rats, probably by reducing leukocyte adhesion to the sinusoidal wall.

DMSO on the World Wide Web

Because DMSO is an organic solvent with multiple applications in industry and medicine, it is readily available throughout the United States. As news of its potential medical applications has spread through lay publications, DMSO has gained popularity in the unregulated world of homeopathic remedies and health and nutrition outlets. It can be purchased in some health food stores and through hundreds (if not thousands) of Web sites at a concentration of 70% or 90% for less than $10.00 for an 8-ounce bottle. Gels and creams are also available. Web sites typically contain a disclaimer, such as this one from www.smartbomb.com: “Ninety-nine % pure DMSO. This product is intended for use as a solvent only. The choice of the process used in the various applications is the sole responsibility of the user.”

Some applications of DMSO touted on the Web are so absurd that they are comical. DMSO and MSM capsules allegedly treat or prevent allergies and asthma, back pain, carpal tunnel syndrome, constipation, diarrhea, depression, diabetes, emphysema, heartburn, hypertension, infection, leg cramps, migraines, parasites, and sinusitis. Further, claims are made that it reduces wrinkles, grows hair in balding areas, and stimulates DNA repair. Unfortunately, these kinds of claims can only confuse the actual and valuable applications of DMSO in medicine.

Concluding Thoughts

The FDA status of DMSO is somewhat reminiscent of the history of silicone gel–filled breast implants. DMSO got a reputation for toxicity in 1965 that has not been overcome, even though studies have determined that lens changes do not occur in humans or other primates treated with DMSO. The lack of approved uses for DMSO may have tragic consequences. Injections of DMSO into the spinal cord soon after injury have shown great promise for restoring function. Furthermore, the use of DMSO for treating closed head injuries is not an option in the United States, and no FDA-approved clinical trials are currently underway.

At the same time, we find no instances of the FDA warning physicians not to use DMSO. Furthermore, since people have the choice of self-medicating with DMSO, it is difficult to imagine a pharmaceutical company willing to do the work required to determine what the actual value of DMSO might be.

Good experimental and anecdotal evidence indicates that DMSO increases tissue perfusion and may effectively treat or prevent ischemia in flaps. The application of DMSO cannot salvage every compromised flap, but we have witnessed its benefits when used on flaps that show signs of ischemia.

References


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