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Methylsulfonylmethane for treatment of low back pain: A safety analysis of a randomized, controlled trial

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ABSTRACT

Objective: To ensure that 16 weeks of methylsulfonylmethane (MSM) does not cause adverse effects in patients with the musculoskeletal disorders of osteoarthritis and back pain.

Design: We carried out a subgroup analysis on data from a randomized, double-blind, placebo-controlled trial, "The use of Methylsulfonylmethane (MSM) in the treatment of low back pain," to determine the safety of taking 6 g daily of MSM (OptiMSM®, Bergstrom Nutrition). We monitored metabolic parameters to determine whether MSM altered hematologic, liver or kidney function. We also monitored physiologic parameters of blood pressure and weight.

Setting: Family Medicine Residency, Mike O'Callaghan Military Medical Center.

Main outcome measures: Metabolic parameters as measured by hematologic function - white blood cells (WBC), platelets, hemoglobin (Hb), glucose; liver function as measured by - total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Physiologic parameters as measured by weight, diastolic (DBP) and systolic blood pressure (SBP); kidney function as measured by creatinine.

Results: Analysis of outcome measures showed no significant difference between MSM and placebo ($p < 0.05$) safety values.

Conclusion: MSM has no effects on WBC, platelets, Hb, total bilirubin, AST, ALT, creatinine weight, DBP, or SBP in this study.

1. Introduction

Methylsulfonylmethane (MSM) is a volatile member of a family of organic sulfur-containing compounds found in the food chains of terrestrial and marine life.[1] It is a water soluble, white, slightly bitter tasting crystalline substance. Manufacturers can produce MSM from a reaction between dimethyl sulfoxide and hydrogen peroxide during which all hydrogen peroxide is consumed. After the reaction, the manufacturer purifies MSM by a distillation process, the product of which is the dietary supplement MSM.

The United States regulates MSM as a dietary supplement. The Food and Drug Administration (FDA) does not regulate MSM as a food additive and has not granted it Generally Recognized as Safe (GRAS) status. However, the specific supplement used in this study, OptiMSM® (Bergstrom Nutrition, IND#122180), is a licensed brand of distilled MSM and is considered GRAS by the FDA.[2]

Many investigators conducted safety studies either in vitro or on animals.[3–5] An acute toxicity study of MSM using a single oral dose of 2000 mg MSM/kg in rats and mice and found no indication of toxicity.[3,4] In a different acute toxicity study on rats, a single dose of 2000 mg MSM/kg by gavage had no adverse effect on rats.[5] It is important to understand MSM's safety profile in humans because a growing population of aging patients are dosing themselves with some form of complementary and integrative medicine substance such as MSM[6] for a variety of conditions. MSM is often advertised as a treatment for osteoarthritis and back pain.

Osteoarthritis (OA) is a degenerative joint disease affecting mainly articular cartilage, and is a leading cause of disability in the United States.[7,8] Back pain has a variety of etiologies and is the leading cause of disability across the world.[9,10] The economic impact of musculoskeletal disorders such as OA and back pain is rising.[11] Aggregate total direct and indirect all-cause expenditures related to musculoskeletal disorders are increasing, as indicated by such metrics as medical costs and wage loss, respectively.[11] Our primary study specifically

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evaluated MSM for the reduction of pain and improvement of function in subjects with osteoarthritis and back pain. This focus addressed the growing desire of patients to escape the traditional pharmaceutical side effects and possible ineffectiveness of conventional western medicine such as nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol.[12,13] Importantly, this safety analysis responded to the need for more rigorous randomized controlled trials evaluating safety of using dietary supplements such as MSM in treating and mitigating musculoskeletal disorders.[14–17]

As such, we conducted a pre-specified analysis of MSM's pharmacodynamics effect on select laboratory and physiological values collected as part of our trial investigating the therapeutic effect of MSM for osteoarthritis and low back pain.

2. Materials and methods

2.1. Study oversight and patient population

This analysis was part of a trial approved by Wilford Hall Ambulatory Surgical Center Institutional Review Board (Protocol # FWH20140075 H). We obtained informed consent from all individual participants included in the study.

Subjects were a combination of active duty military members and their families and retired military members and their families on one United States Air Force Base installation. The Air Force medical treatment facility treats the full range of ages and medical conditions. We included patients between the ages of 18 and 65 with symptoms of low back pain lasting greater than 12 weeks. We excluded patients if they had lower back pain caused by infection, tumor, osteoporosis, ankylosing spondylitis, fracture, deformity, known autoimmune process, or cauda equina syndrome. We did not enroll patients who met the criteria for surgery as indicated by progressive motor deficit, sphincter impairment from neurological cause, or who had disabling sciatic pain in the absence of backache lasting 6 weeks or more attributed to a compromised nerve root and demonstrated by magnetic imaging or computer tomography. We also excluded patients with treated or untreated central nervous system impairment; oncologic disease during the previous 5 years; unexplained weight loss, fever, or chills; diagnosed upper urinary tract infection within the last 28 days; history of intravenous drug use; immunocompromised host; sciatica; history of bleeding disorders; history of high blood pressure; history of heart, kidney, liver, or ulcer disease; allergic to analgesics or NSAIDs; pregnant or breastfeeding; initial pain greater than 8/10 on initial intake evaluation; or Comprehensive Metabolic Panel (CMP) with values outside safe range. Additionally, we excluded those with a severe comorbidity such as a detriment to the patient's wellbeing, cirrhosis, or ongoing dialysis. Unless patients agreed to a 2-week washout period, we did not allow those taking muscle relaxers, tramadol, gabapentin, pregabalin, glucosamine, narcotic pain medications, or NSAIDs to participate in our study.

2.2. Study design

We designed this trial as a randomized, double-blind, placebo-controlled trial to determine whether 6 g daily of MSM (OptiMSM®, Bergstrom Nutrition) plus standard of care naproxen improves symptoms of lower back pain versus standard of care naproxen plus placebo. We monitored metabolic parameters to determine whether MSM altered hematologic, liver or kidney function. We monitored physiologic parameters of blood pressure and weight as well.

At the beginning of the study, we assigned subjects to one of two groups; randomization was balanced using stratified random sampling with proportionate allocation to ensure that we represented all aspects of the population in the sample. After enrollment, we randomized subjects into 16 weeks of therapy with either six grams of MSM plus standard of care naproxen or placebo plus standard of care naproxen.

Table 1
Demographics.

	MSM + Naproxen		Placebo + Naproxen	
Age (years)	**N**	**Mean**	**N**	**Mean**
	46	35	40	36
Race/Ethnicity	**N**	**%**	**N**	**%**
Asian	3	6.5	2	5
Black	9	19.6	6	15
Pacific Islander/American Indian/Alaskan Native	1	2.1	0	0
White	21	45.7	25	62.5
Other or undefined	8	17.4	2	5
Hispanic, Latin or Mediterranean	4	8.7	5	12.5
Sex	**N**	**%**	**N**	**%**
Female	16	34.8	11	27.5
Male	30	65.2	29	72.5

The Food and Drug Administration granted an investigator-initiated Investigation New Drug status (#122180) to the MSM used in this study. Through a third party laboratory, we analyzed both a sample of the MSM and the rice flour placebo and found them free of toxins and adulterants. Bergstrom Nutrition and Health Wright Products, Inc. encapsulated the intervention and placebo in identical clear two-piece hard shell vegetable capsules. Health Wright Products bottled and labeled the MSM and placebo.

One hundred patients were enrolled in this study—46 in MSM + Naproxen and 40 in placebo + naproxen completed the study. Patient characteristics are shown in Table 1 and distribution/randomization is summarized in Fig. 1.

2.3. Assessments and endpoints

2.3.1. Physiological tests

We recorded weight (pounds), systolic blood pressure (SBP) (mmHg), and diastolic blood pressure (mmHg) (DBP) at screening visit, time zero, 4 weeks, 8 weeks, 12 weeks, and 16 weeks.

2.3.2. Laboratory tests

We required subjects to undergo blood tests at the screening visit/time zero, 4 weeks, 8 weeks, 12 weeks, and 16 weeks. We specifically drew a CMP and Complete Blood Count (CBC). For this safety study, we considered the following values: white blood cell count (WBC), hemoglobin A1C, platelets, glucose, creatinine, total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

2.3.3. Endpoints

We used the physiological and laboratory tests outlined in Sections 2.3.1 and 2.3.2 as endpoints for our study and sought to determine there was no statistical change in values over time.

2.4. Statistical analysis

2.4.1. Sample size determination

A sample size estimation indicated that thirty-four subjects per group with five repeated measures would achieve a power of 0.80 to detect a large effect size of 0.40 at $\alpha = 0.05$. The power for the rANCOVA was assessed using G*Power Version 3.0.10 76.[18] The investigators anticipated there would be large effect size as determined by a 50% improvement in clinical outcomes.

2.4.2. Pharmacodynamic analyses

We conducted a pharmacodynamic analysis of MSM. We used rANOVA for treatment and time, controlling for within subject variation and naproxen doses (high, low). We also conducted a post hoc power analysis for all outcomes in order to estimate the effect size.

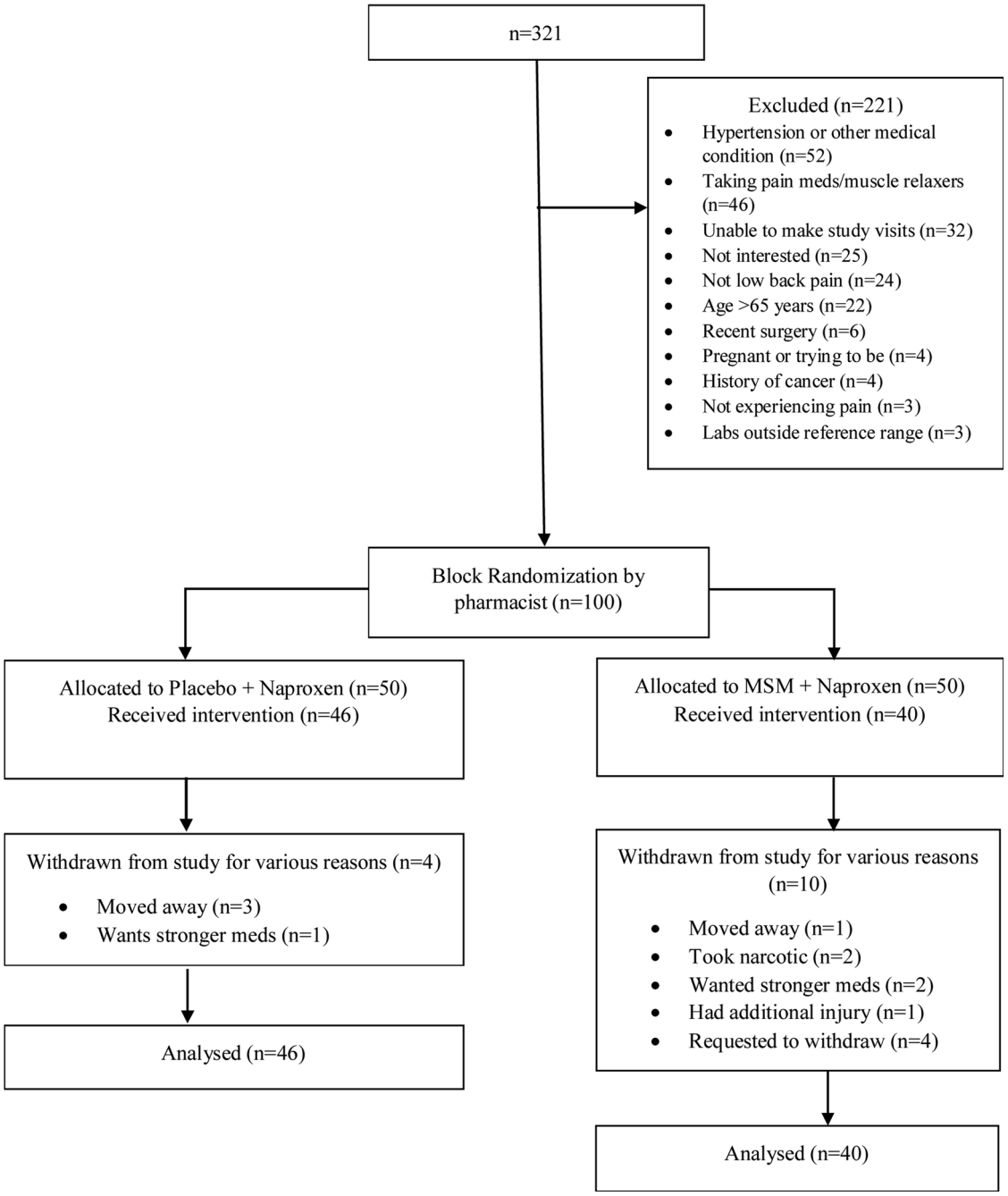

Fig. 1. Patient Distribution.

3. Results

One hundred patients were enrolled in this study—50 in MSM + Naproxen and 50 in placebo + naproxen. Table 1 shows subject characteristics and distribution/randomization are summarized in Fig. 1.

We did not measure the pharmacokinetics of MSM. We did measure the pharmacodynamics of MSM as outlined in the previous Section 2.4.2. Using the rANOVA, we found no significant difference between MSM and placebo in any variable (see Table 2).

4. Discussion

Other investigators have conducted in vitro and animal in vivo studies probing the safety of MSM. This is the first study that investigates MSM safety in human subjects. This is critical since dietary supplement companies often do not perform studies necessary to ensure safety. Our study helps bridge the gap between the consumer and the supplement industry to support the safe consumption of potentially beneficial products.

This study demonstrates that MSM is probably safe. The range of physiologic and laboratory measures recorded give reassurance that MSM has no negative effect on a wide variety of body systems over the course of 16 weeks. While patients may choose to consume this product on their own for longer than this, we have demonstrated that over the course of 16 weeks that this can be done with reasonable reassurance of no negative effects on their physiology. While there was a slight difference in the genetic background of those assigned to the placebo arm, this was the result of blinded randomized assignment. However, even with this variation, the pre vs post measured values within these groups

Table 2
Effect of Methylsulfonylmethane on physiologic values and biomarkers.

	MSM + Naproxen Pre-intervention (N = Mean + /-SD	MSM + Naproxen Post-intervention (N = Mean + /-SD	Placebo + Naproxen Pre-intervention(N = Mean + /-SD	Placebo + Naproxen Post-intervention (N = Mean + /-SD	rANOVA Treatment:Doses:Time p value
SBP	123(11)	121(12)	122(11)	122(11)	0.72
DBP	81(9)	79(9)	79(10)	77(8)	0.29
Weight	181(33)	182(34)	194(30)	196(31)	0.16
WBC	7.1(1.7)	7.2(2.1)	6.6(2.0)	6.4(1.6)	0.99
Hemoglobin	14.8(1.4)	14.6(1.4)	14.8(2.0)	14.8(1.5)	0.26
Platelets	270(60)	271(61)	261(59)	257(51)	0.72
Glucose	95(11)	97(11)	93(9)	94(12)	0.10
Creatinine	1.0(0.2)	1.0(0.2)	1.0(0.2)	1.0(0.2)	0.76
Total Bilirubin	0.6(0.3)	0.6(0.3)	0.6(0.3)	0.6(0.3)	0.90
ALT	29(17)	31(18)	28(13)	28(19)	0.24
AST	22(12)	21(7)	21(8)	22(13)	0.50

showed no change, again suggesting safety for 16 weeks. Average age in this study reflects that of those receiving care though this military base. A further strength of this study is the concurrent administration of naproxen to all participants since this mimics actual patient practices where patients often take multiple over-the-counter medications and supplements that could interact.

There are several limitations of this study. First, as a clinical trial, we excluded people with complex medical conditions; thus, we can only draw conclusions in relatively healthy persons. Second, we only measured biomarkers for 16 weeks while patients may take MSM for years, thus we are unable to draw conclusions about the long-term safety of MSM.

5. Conclusion

Our study suggests that daily consumption of six grams of MSM for sixteen weeks did not have a significant effect on weight, SBP, DBP, WBC, hemoglobin, platelets, glucose, creatinine, total bilirubin, ALT, or AST. Future alternative medicine safety trials should consider concurrent administration of other typical treatments to add ecological validity to their data.

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References

1. Lovelock JE, Maggs RJ, Rasmussen RA. Atmospheric dimethyl sulphide and the natural sulphur cycle. *Nature.* 1972;237.
2. *Agency response letter GRAS notice No. GRN 000229*. fda.gov.; 2017.
3. Yu P, Peano S. *LIGNISUL MSM. "Single dose toxicity study in mice by oral route" RBM EXP. No. 980175.* Torino, Italy: LCG bioscience RBM laboratory; 2000.
4. Yu P, Peano S. *LIGNISUL MSM. "Single dose toxicity study in rats by oral route" RBM EXP. No. 980174.* Torino, Italy: LCG bioscience RBM laboratory; 2000.
5. Horvath K, Noker PE, Somfai-Relle S, Glavits R, Financsek I, Schauss AG. Toxicity of methylsulfonylmethane in rats. *Food Chem Toxicol.* 2002;40:1459–1462.
6. Basedow M, Runciman WB, March L, Esterman A. Australians with osteoarthritis; the use of and beliefs about complementary and alternative medicines. *Complement Ther Clin Pract.* 2014;20:237–242.
7. *Chronic rheumatic conditions*. World Health Organization; 2016 www.who.int/chp/topics/rheumatic/en/ November 17.
8. Neogi T, Zhang Y. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am.* 2013;39:1–19.
9. Hartvigsen J, et al. Low back pain series: what low back pain is and why we need to pay attention. *Lancet.* 2018;391(June Issue 10137):2356–2367.
10. Hoy D, March L, Brooks P, et al. *The global burden of low back pain: estimates from the Global Burden of Disease 2010 study Annals of the Rheumatic Diseases Published Online First: 24 March.* 2014; 2014https://doi.org/10.1136/annrheumdis-2013-204428.
11. United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS), Fourth Edition, forthcoming. Rosemont, IL. Available at http://www.boneandjointburden.org.
12. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ.* 2015;350:h1225.
13. Machado GC, Ferreira M, Pinheiro M, Shaheed CA, Maher G. Paracetamol for low back pain. *Cochrane Database Syst Rev.* 2016;2016(June 6):CD012230.
14. Liu Xiaoqian, Eyles Jillian, McLachlan Andrew J, Mobasheri Ali. Which supplements can I recommend to my osteoarthritis patients? *Rheumatology.* 2018;57(May suppl. 4):iv75–iv87. https://doi.org/10.1093/rheumatology/key005.
15. Brien S, Prescott P, Bashir N, Lewith H, Lewith G. Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthr Cartil.* 2008;16:1277–1288.
16. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. *Brit J Sports Med.* 2018;52:167–175.
17. Brien S, Prescott P, Lewith G. Meta-analysis of the related nutritional supplements dimethyl sulfoxide and methylsulfonylmethane in the treatment of osteoarthritis of the knee. *Evid Based Complement Alternat Med.* 2011;2011:528403.
18. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39(2):175–191.