ORIGINAL ARTICLE

Effects of nicardipine versus diltiazem on catecholamine secretion and renin-angiotensin-aldosterone system during isoflurane anesthesia

Tomoki Nishiyama, MD, PhD

Department of Anesthesiology, Shinagawa Shishokai Hospital, 1-29-7, Kita-Shinagawa, Shinagawa-ku, Tokyo, 140-0001, (Japan)

Correspondence: Tomoki Nishiyama, MD, PhD:, Department of Anesthesiology, Shinagawa Shishokai Hospital, 1-29-7, Kita-Shinagawa, Shinagawa-ku,Tokyo, 140-0001, (Japan); Tel. +81-3-5781-0700; Fax. +81-3-5781-0828; E-mail: nishit-tky@umin.ac.jp

ABSTRACT

Background: Nicardipine and diltiazem might have different actions on hemodynamics, catecholamine secretion and hormonal response during anesthesia. However, there have been no studies to compare these effects between nicardipine and diltiazem during general anesthesia. The present study was performed to compare the effects on hemodynamics, catecholamine secretion and hormonal response between nicardipine and diltiazem in isoflurane anesthesia.

Methodology: Twenty patients who received resection of brain tumor were divided into two groups□Anesthesia was induced with thiopental and fentanyl. Anesthesia was maintained with isoflurane 0.5 to 1.5% and 67% nitrous oxide in oxygen. After microsurgical procedure started and when hemodynamics were stable, nicardipine 1 mg or diltiazem 10 mg were administered in one minute. Blood pressure, heart rate, and plasma concentrations of epinephrine, norepinephrine, angiotensin I and II, aldosterone, and renin activity were measured for 30 min. During the study period, isoflurane concentration was kept constant.

Results: Blood pressure decreased significantly in one minutes in both groups, and the decrease continued for 10 min in the nicardipine group and for 30 min (study periods) in the diltiazem group. Heart rate significantly increased at 1 to 10 min in the nicardipine group and decreased at 5 to 30 min in the diltiazem group. Blood pressure and heart rate were significantly lower in the diltiazem group at 5 to 30 min. Plasma epinephrine and norepinephrine concentrations increased significantly in the nicardipine group but did not change in the diltiazem group, and significantly lower at 10 to 30 min in the diltiazem group. Plasma renin activity and concentrations of angiotensin I and II, and aldosterone did not change and had no differences between the groups.

Conclusion: To decrease blood pressure in isoflurane anesthesia, nicardipine should be used when sympathetic activation is favorable, while diltiazem should be used to decrease heart rate without increase of sympathetic activity.

Key words: Isoflurane, Catecholamine, Renin-angiotensin-aldosterone system

Citation: Nishiyama T. Effects of nicardipine versus diltiazem on catecholamine secretion and renin-angiotensin-aldosterone system during isoflurane anesthesia. Anaesth Pain & Intensive Care 2014;18(4):332-337

INTRODUCTION

Nicardipine and diltiazem are often used to decrease blood pressure during general anesthesia. We already know that the effects of nicardipine on hemodynamics during general anesthesia are different among different inhalation anesthetics, enflurane, isoflurane, or sevoflurane.[1] In addition, nicardipine increases[2] but diltiazem decreases[3] heart rate. These different effects might be modified by inhalation anesthetics. Furthermore, hemodynamic changes induced by these agents might have some effects on hormonal changes such as catecholamine secretion and renin-angiotensin-aldosterone system. We know that nicardipine and

diltiazem have different effects on hemodynamics and catecholamine secretion in sevoflurane anesthesia.[4] However, there have been no studies to compare these changes during isoflurane anesthesia. Isoflurane has been widely used as an inhalation anesthetic, therefore, the present study was performed to compare the effects of nicardipine and diltiazem on hemodynamics, catecholamine secretion, and renin-angiotensin-aldosterone system during isoflurane anesthesia.

METHODOLOGY

This study is a non-blinded randomized study. After the approval of the Ethical Committee of the hospital and written informed consent from patients, 20 patients aged 50 to 70 years with ASA physical status I or II, who would receive resection of brain tumor were divided into two groups randomly by an envelope method. Those with cardiac, liver, renal, or hormonal disease such as diabetes, hyperthyroid, etc., obesity (body mass index > 30), allergy to diltiazem or nicardipine, and who had drug abuse were excluded.

Without premedication, anesthesia was induced with thiopental 5 mg/kg and fentanyl 4 μg/kg. Endotracheal intubation was facilitated with vecuronium 0.2 mg/kg. Anesthesia was maintained with isoflurane 0.5 to 1.5% and 67% nitrous oxide in oxygen. Radial artery was cannulated to measure blood pressure. Lactated Ringers solution was infused to keep urine volume more than 1 ml/kg/h. Mannitol 20% 300 ml was infused after craniotomy. Ventilation was adapted to keep end-tidal carbon dioxide tension between 30 and 35 mmHg.

After microsurgical procedure started and when hemodynamics were stable as ±5% variation for 30 min, nicardipine 1 mg or diltiazem 10 mg was administered in one minute. Blood pressure, heart rate, and plasma concentration of epinephrine, norepinephrine, angiotensin I and II, and aldosterone, and renin activity were measured for 30 min. During the study period, isoflurane concentration was kept constant and no other agents were administered. Plasma concentration of epinephrine and norepinephrine were measured with high-performance liquid chromatography. Plasma concentrations of angiotensin I, II, and aldosterone, and plasma renin activity were measured with radioimmunoassay.

Data were shown as mean±standard deviation or number of the patients. Power analysis was performed to detect the intra- and inter- group differences of measured parameters with power of 0.90 using G Power™ software (University Mannheim, Germany). Statistical analysis was performed with the chi-square test and factorial analysis of variance (ANOVA) for demographic data, and repeated ANOVA for measured parameters followed by Student-Neuman-Keuls test as a post hoc analysis. A p value less than 0.05 was considered to be statistically significant.

RESULTS

By power analysis, 18 patients were necessary in total, therefore, 20 patients were studied. Demographic data and isoflurane concentration at the start of the study were not different between the two groups (Table 1).

Table 1: Demographic data and isoflurane concentration

Variable	Nicardipine	Diltiazem
Age (years)	62 ± 6	61 ± 7
Gender (male/female)	6/4	4/6
Body weight (kg)	65 ± 13	59 ± 14
Duration of surgery (min)	394 ± 57	371 ± 76
Interval between start of surgery and start of the study (min)	115 ± 10	119 ± 11
Isoflurane concentration at the time of the study (MAC)	0.7 ± 0.2	0.7 ± 0.1

Mean ± standard deviation or number of the patients; MAC, minimum alveolar concentration

Blood pressure decreased significantly in one minute in both groups, and the decrease continued for 10 min in the nicardipine group and for 30 min (study periods) in the diltiazem group (Figure 1-1). Blood pressure was significantly lower in the diltiazem group at 5 to 30 min than in the nicardipine group. Heart rate significantly increased at 1 to 10 min in the nicardipine group and decreased at 5 to 30 min in the diltiazem group (Figure 1-2). Heart rate was significantly lower at 5 to 30 min in the diltiazem group than in the nicardipine group. Plasma epinephrine and norepinephrine concentrations significantly increased in the nicardipine group but did not change in the diltiazem group, and were significantly lower at 10 to 30 min in the diltiazem group (Figure 2-1, 2-2). Plasma renin activity, angiotensin I and II and aldosterone concentrations did not change significantly in both groups, and did not have any differences between the two groups (Figure 3-1, 3-2, 3-3, 3-4).

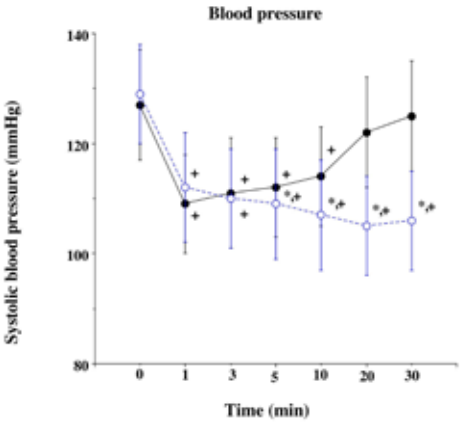


Figure 1-1: Comparison of systolic blood pressure (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group
*: P < 0.05 vs. nicardipine group; +: P < 0.05 vs. the value at time 0

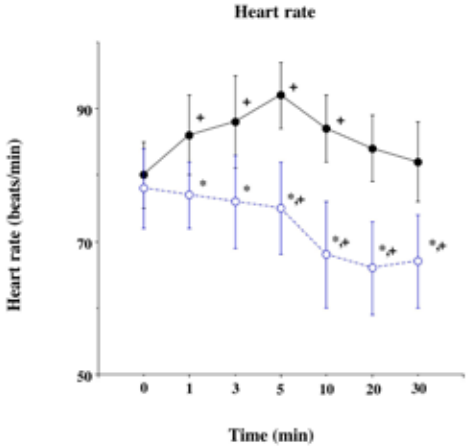


Figure 1-2: Comparison of heart rate (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group
*: P < 0.05 vs. nicardipine group; +: P < 0.05 vs. the value at time 0

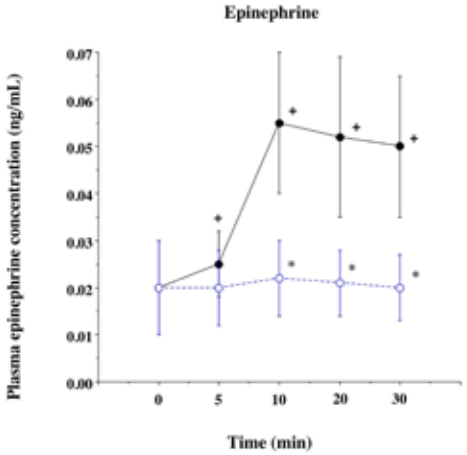


Figure 2-1: Comparison of plasma epinephrine concentration (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group
*: P < 0.05 vs. nicardipine group; +: P < 0.05 vs. the value at time 0

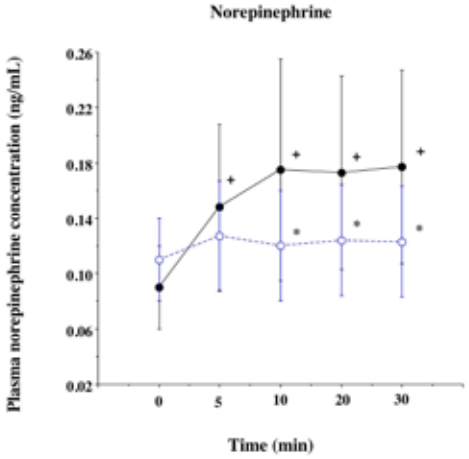


Figure 2-2: Comparison of norepinephrine concentration (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group
*: P < 0.05 vs. nicardipine group; +: P < 0.05 vs. the value at time 0

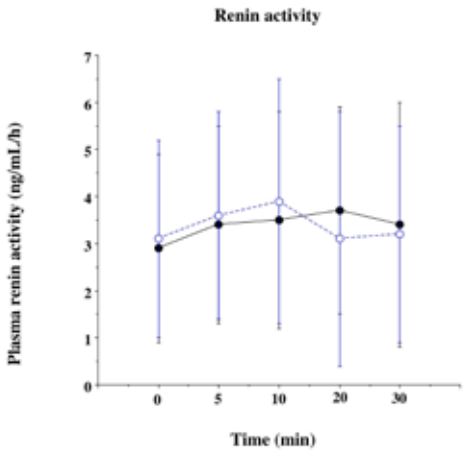


Figure 3-1: Comparison of Plasma Renin activity (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group

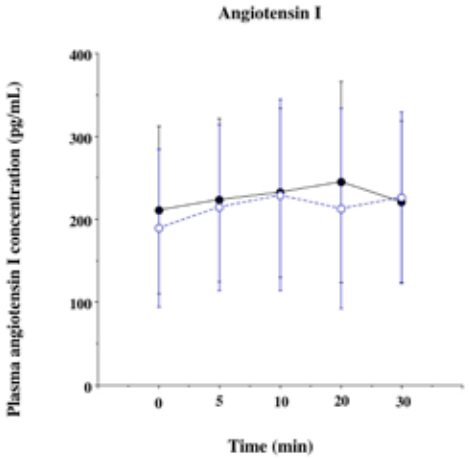


Figure 3-2: Comparison of angiotensin I concentration (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group

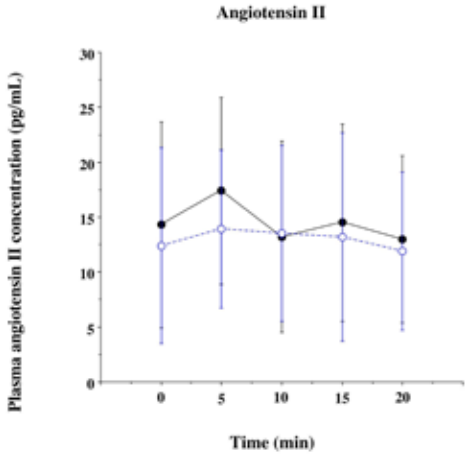


Figure 3-3: Comparison of angiotensin II (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group

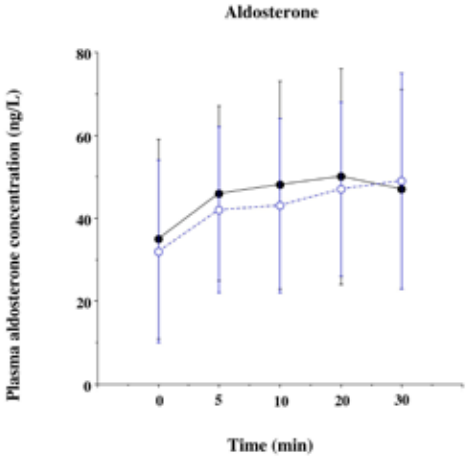


Figure 3-4: Comparison of aldosterone concentration (Mean ± SD)
●—● nicardipine group; ○—○ diltiazem group

DISCUSSION

The present results showed that during isoflurane anesthesia, both nicardipine and diltiazem decreased blood pressure, but nicardipine increased heart rate and plasma concentrations of epinephrine and norepinephrine, while diltiazem decreased heart rate with no changes in plasma concentrations of epinephrine and norepinephrine. Renin-angiotensin-aldosterone system did not change by both nicardipine and diltiazem.

There are some limitations of this study. This study should be done during a hypertensive episode during surgery, but it is quite difficult to study in such situation. In addition, hypertensive episode might have large variations among patients. Therefore, we performed this study in stable hemodynamic condition. Thus, the results of this study cannot be applied in clinical situation when we need to use nicardipine or diltiazem. Nicardipine and diltiazem were administered as a fixed dose of 1 mg and 10 mg, respectively, not by per kg in body weight. This is because clinically these doses are usually administered to decrease blood pressure during general anesthesia, not by per kg basis. Therefore, the dose per kg will be different in each patient, but no difference in body weight between the groups suggested the results were comparable between the groups. Data collection was only for 30 min, which was too short to detect the hormonal changes, but to keep constant inhalation concentration under constant surgical stimuli, 30 min was the limit. In addition, this is not a blind study because of the safety reason. However, plasma concentrations were measured later at the laboratory where the laboratory workers were not aware of the agent administered.

Nicardipine decreased blood pressure and increased heart rate with increased plasma concentrations of epinephrine and norepinephrine during isoflurane anesthesia in our previous study,[1] which is consistent with the present results, while duration of the changes were different probably due to different anesthesia levels and surgical stimuli between the studies. Chelly et al[5] reported that isoflurane increases hypotension by nicardipine, but inhibits reactive increase in heart rate. We had no control without isoflurane, therefore, we could not see whether isoflurane increased the effects of nicardipine, but heart rate increased in our study. Isoflurane inhibits parasympathetic activity more than sympathetic activity,[6] which might increase heart rate. Morooka et al[8] concluded that nicardipine inhibited hypotension induced adrenal catecholamine release. However, in their study, plasma epinephrine and norepinephrine concentrations increased by nicardipine as our results.

Nicardipine increases plasma renin activity, which results from a baroreflex stimulation of juxtaglomerular cells rather than a direct action on release mechanisms,[9] which may counteract the inhibitory effect of aldosterone by nicardipine.[10] It was reported that acute administration of oral nicardipine increased plasma aldosterone levels at 1 hr and they returned to the baseline in 4 hrs.[11] We used bolus intravenous administration of nicardipine, which has not been studied. Therefore, it is difficult to compare previous studies[9-11] with the present results.

Diltiazem inhibits sinus pacemaker and atrioventricular conduction,[8] so it decreased heart rate. The depressant effects of diltiazem and isoflurane on sinoatrial function are reported to be additive.[12] The combination of diltiazem and isoflurane results in depression of cardiac function.[13] During isoflurane anesthesia, the vasodilating effects of diltiazem were not observed, but diltiazem decreased left ventricular performance.[13] Thus, blood pressure and heart rate decreased with diltiazem in the present study, while in sevoflurane anesthesia in our previous study,[4] sevoflurane might inhibit the effects of diltiazem on sinus pacemaker and atrioventricular conduction, thus heart rate did not change. Diltiazem acts on sympathetic nerves system and releases norepinephrine.[14] The blood pressure decrease by diltiazem was inversely correlated to logarithm of plasma norepinephrine concentration in rat study.[15] However, Isojima et al reported that diltiazem decreased the secretion of epinephrine and norepinephrine, especially norepinephrine,[16] as shown by decrease of epinephrine concentration by diltiazem in sevoflurane anesthesia in our previous study.[4] The present study showed no changes in plasma epinephrine and norepinephrine concentrations with diltiazem in isoflurane anesthesia. Therefore, the activation of sympathetic nervous system by decrease in blood pressure and heart rate, and inhibition of secretion of epinephrine and norepinephrine might offset each other in isoflurane anesthesia. Infusion of diltiazem did not affect renin-angiotensin-aldosterone system during droperidol-fentanyl anesthesia,[17] which is consistent with the results in isoflurane anesthesia in the present study.

CONCLUSION

In conclusion, to decrease blood pressure in isoflurane anesthesia, nicardipine should be used when sympathetic activation is favorable, while diltiazem should be used to decrease heart rate without increase of sympathetic activity. Renin-angiotensin-aldosterone system did not change by bolus nicardipine or diltiazem in isoflurane anesthesia.

Conflict of interest: I declare that this study was not funded by any agency and there is no conflict of interest.

REFERENCES

1. Nishiyama T, Matsukawa T, Hanaoka K, Conway CM. Interactions between nicardipine and enflurane, isoflurane, and sevoflurane. Can J Anaesth 1997;44:1071-1076. [PubMed]
2. 2. Turlapaty P, Vary R, Kaplan JA. Nicardipine, a new intravenous calcium antagonist: A review of its pharmacology, pharmacokinetics, and perioperative applications. J Cardiothorac Anesth 1989;3:344-355. [PubMed]
3. Fujimoto T, Peter T, Mandel WJ. Electrophysiological and hemodynamic action of diltiazem: Desparate temporal effects shown by experimental dose-response studies. Am Heart J 1981;101:403-407. [PubMed]
4. Nishiyama T. Effects of nicardipine and diltiazem on catecholamine secretion and renin-angiotensin-aldosterone system during sevoflurane anesthesia. Analg Resusc Curr Res 2014;3:1 doi: 10.4172/2324-903X.1000110
5. Chelly JE, Hysing ES, Abernethy DR, Doursout MF, Hartley CJ, Guerret M, et al. Role of isoflurane on hemodynamic properties and disposition of nicardipine. J Pharmacol Exp Ther 1987;241:899-906.
6. [PubMed] [Free full text]
7. Yli-Hankala A, Randell T, Seppala T, Lindgren L. Increases in hemodynamic variables and catecholamine levels after rapid increase in isoflurane concentration. Anesthesiology 1993;78:266-271. [PubMed]
8. Morooka H, Gotoh S, Makita T, Fukuzaki M, Shibata O, Gotoh Y. Adrenal catecholamine releases during hypotension with continuous administration of calcium entry blockers and nitroglycerin. Masui (Jpn J Anesthesiol) 1992;41:1070-1075. [PubMed]
9. Katz AM. Basic cellular mechanisms of action of the calcium-channel blockers. Am J Cardiol 1985;55:2B-9B. [PubMed]
10. Wu KD, Hsieh BS, Chu TS, Yen TS. The acute effect of nicardipine on the renin-angiotensin-aldosterone system in salt-sensitive essential hypertension. Clin and Exper Hypertension 1993;15:185-196. [PubMed]
11. Damasceno A, Santos A, Pestana M, Serrão P, Caupers P, Soares-da-Silva P, et al. Acute hypotensive, natriuretic, and hormonal effects of nifedipine in salt-sensitive and salt-resistant black normotensive and hypertensive subjects. J Cardiovasc Pharmacol. 1999 Sep; 34(3):346-53. [PubMed]
12. Clifton GG, Cook ME, MacCarthy P, Bienvenu G, Walsh M, Turlapaty P, et al. Changes of plasma renin activity and atrial natriuretic factor during intravenous nicardipine treatment of severe hypertension. Int J Clin Pharmacol Ther Toxicol 1989;27:578-582. [PubMed]
13. Priebe HJ, Skarvan K. Cardiovascular and electrophysiologic interactions between diltiazem and isoflurane in the dog. Anesthesiology 1987;66:114-121. [PubMed]
14. Kapur PA, Campos JH, Tippit SE. Influence of diltiazem on cardiovascular function and coronary hemodynamics during isoflurane anesthesia in the dog: correlation with plasma diltiazem levels. Anesth Analg 1986;65:81-87. [PubMed]
15. Wolchinsky C, Zsoter TT. The effect of diltiazem on noradrenaline release. Br J Pharmac 1985;85:387-393. [PubMed] [Free full text]

16. Higashidate S, Imai K, Prados P, Adachi-Akahane S, Nagao T. Relations between blood pressure and plasma norepinephrine concentrations after administration of diltiazem to rats: HPLC-peroxyoxalate chemiluminescence determination on an individual basis. Biomed Chromatograph 1994;8:19-21. [PubMed]
17. Isojima K, Takase B, Arakawa K, Shibuya T, Satomura K, Mizuno K, et al. Effects of diltiazem on hemodynamics, plasma catecholamine and Renin activity during exercise in hypertension. J Cardiol 1991;21:383-390. [PubMed]
18. Kono K, Okutani R, Tsuda S, Ishida H, Nakamura H, Philbin DM. Effects of diltiazem on Renin-aldosterone and ACTH-adrenocortical function during upper abdominal surgery. J Clin Anesth 1990;2:407-414. [PubMed]

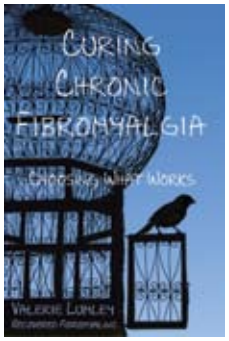
★★★★★

MY MOST UNFORGETABLE EXPERIENCE

Fibromyalgia – out of the dark tunnel

Valerie Lumley*

*Recovered fibromyalgic and author of "Curing Chronic Fibromyalgia – Choosing What Works"



Contrary to popular belief, fibromyalgia (FMS) is curable. Curing this condition led me to discover that FMS is a syndrome caused by a chronic brainstem injury, which over time distorts the signals from the brain into the body and back again that regulate all biological functions, and causes the entire central nervous system to become hyperactive and hypersensitive at the same time.

Brainstem injury occurs as a result of a major trauma, or several compounding minor traumas over time, to the neck and spine. The most common source of brainstem injury is the Atlas (C-1) misalignment, caused by whiplash. Other causes include a blow to the head, a fall, a lifting accident, and even chronic poor posture, carrying heavy babies, or a poor golf swing.

During exhaustive scientific research for writing this book, I educated myself widely, and used myself as a case study as I cured this disorder. I turned to alternative medicine for many answers. The result was a clear, definitive road map leading back into life again for millions of FMS sufferers worldwide. My success in curing this condition is a proof it can be done.

When looking back, I can remember what it felt like to be completely disabled by pain, depressed from sleep deprivation, energy bankruptcy and hopelessness, and unable to see past the next moment I was trying to survive. I was bedridden for 2 years and housebound for 10. It took me 4 years to get well after initiating my protocol for a lasting cure that is maintainable and real. It all seems like an unbearable, horrific nightmare that I finally woke up from.

Now, after benign well from FMS for nearly five years, I am only left with two lower cervical vertebrae that are degenerated from 13 years of pressure from a misaligned Atlas (C-1), now aligned and holding, and a couple stress points in my spine that need periodic adjusting due the scoliosis caused by the Atlas subluxation that is now aligned as well.

My ADL's (activities of daily living) have normalized and I am leading a vibrant, dynamic life, however the stress points in my spine do not always hold up to the demands being made on them from my activities, however, this does not hamper me significantly. My chiropractor keeps me well aligned and my health is no longer compromised.

I have returned to my former singing career as a classical soprano, performing in my own one-woman classical concert series "Viva La Diva – Keeping the Songs Alive" and am studying with a grand master of voice and performance.

I am finding the only obstacle in my path to reaching FMS sufferers is the failed hope they experience being let down by so many caregivers and medical professionals, owing to the fact that the medical profession offers no hope, no explanation of cause or knowledge of cure, and only recommends drugs to manage symptoms for the rest of their lives while their condition continues to degenerate and cause an unnecessary premature death.

The protocol begins with chiropractic aligning the Atlas and spinal subluxations its misalignment causes by an experienced upper cervical chiropractor. It goes on to include classical, constitutional homeopathy, warm water pool therapy, specific nutritional therapy and supplements, psychotherapy, a firm grasp of reality, and the courage to take charge of the condition. Healing this condition means complete rehabilitation of the entire mind and body.

My book tells my story of how I navigated the labyrinth of allopathic and alternative medicine to discover my right healing combination. It fully explains my protocol for a lasting cure that is maintainable and real.

Fibromyalgia is a dark, terrifying tunnel where its sufferers get lost in despair. I want to stand at the end of this tunnel and shine a light bright enough for all to see, and show them how to lead themselves back out into life again. This is my mission: to spread the word of REAL hope.

(The book is endorsed by the International Chiropractic Association, The National Upper Cervical Chiropractors Association, The International Massage Association, The National Association of Acupuncture, Oregon Health and Science University's Fibromyalgia Information Foundation, and enjoys a 5 star review on Amazon, Kindle, and Barns and Nobel.) **www.thefibrocure.com**