TREATMENT OF CEREBRAL INFARCTION

EXPERIMENTAL AND CLINICAL STUDY

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SPRINGER-VERLAG
WIEN NEW YORK

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With 240 partly colored Figures

Library of Congress Cataloging-in-Publication Data. Suzuki, Jiro, 1924– . Treatment of cerebral infarction. Bibliography: p. Includes index. 1. Brain-Infarction. I. Title. [DNLM: 1. Cerebral Infarction. 2. Cerebral Ischemia. WL 355 S968t]. RC394.I5S89 1987. 616.8'1. 86-29758

ISBN 3-211-81933-9 Springer-Verlag Wien — New York
ISBN 0-387-81933-9 Springer-Verlag New York — Wien

PREFACE

It is a great honor and pleasure for me to have Springer-Verlag publish this volume entitled "Treatment of Cerebral Infarction". I am much indebted to my colleagues for my success in publishing this book.

I have engaged in clinical work in the field of neurosurgery for these few decades and I have performed more than 5,000 major operations of intracranial surgery. Throughout this time, it has been my privilege to conduct a 2-hour-morning research seminar in our department every Wednesday and to supervise a great deal of research. At these seminars my fellow research workers and I have exchanged many ideas about the study of neurosurgery and we have designed many animal experiments. The results of the research performed in the previous week have always been reported at such seminars and research workers have benefited from the advice and criticisms given there.

In 1969 I found that the permissible occlusion time for cerebral blood flow could be prolonged by mannitol. In that year Dr. Takashi Yoshimoto started a difficult series of animal experiments to prove my hypothesis. Since then, many researchers have joined our department and many research programs and experiments on cerebral infarction have been carried out. Dr. Yoshimoto hoped that the results of research done in our department over the last sixteen years concerning cerebral infarction could be published. Moved by his enthusiasm, my colleagues took their share in writing each article. I suggested to them that this volume should cover primarily the results of our own research, but that at the same time it should also include the results of related work done by neurosurgical experts throughout the world. Therefore, I hope that this book will interest many investigators who have devoted themselves to research in the field of neuroscience.

My colleagues acknowledge that our research has been stimulated and promoted by our weekly "think tank" sessions and that any achievement we may have attained is due largely to those fruitful discussions. This is the reason why this book is of my authorship. I am very happy and honored that my own contribution to our study of neurosurgery is thus recognized, but I am very conscious that this book was completed thanks to the cooperation of the clinical neurosurgeons who have studied and engaged in clinical neurosurgery with me in Sendai. I must therefore mention those who took part in writing this book: Dr. Takashi Yoshimoto (Chap

ter 1), Dr. Takao Watanabe and Dr. Michiyasu Suzuki (Chapter 2), Dr. Hirobumi Seki (Chapter 3), Dr. Takamasa Kayama (Chapter 4), Dr. Shigeki Imaizumi (Chapter 5), Dr. Kazuo Mizoi (Chapter 6), Dr. Akira Ogawa and Dr. Tetsuo Kogure (Chapter 7), Dr. Satoru Fujiwara (Chapter 8), Dr. Takehide Onuma and Dr. Yoshihide Nagamine (Chapter 9A), Dr. Motonobu Kameyama (Chapter 9B), Dr. Yoshiharu Sakurai (Chapter 9C), Dr. Hiroshi Niizuma (Chapter 10), Dr. Ryuichi Katakura and Dr. Ryuichi Konda (Chapter 11), Dr. Akira Takahashi (Chapter 12), Dr. Taisuke Otsuki and all neurosurgeons who have studied with me in Sendai. I am also grateful to Dr. D. H. Waterbury, who helped us by reading the manuscript and by giving valuable advice on the linguistic problems of English. Especially without the genuine help of Mr. N. D. Cook, as a translator, this book would have never appeared. Finally, I heartily thank Dr. S. Weingärtner and Mr. R. Wieder of the Editorial Department of Springer-Verlag who encouraged us to publish this volume.

Jiro Suzuki

Nagamachi, Sendai
November, 1986

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INTRODUCTION

Among the developed nations, cerebrovascular disease (CVD) ranks as one of the top three causes of human death and must therefore be considered a major health hazard for mankind. Due to the elucidation of the risk factors involved, there has been a gradual decrease in the incidence of hemorrhagic CVD, but together with the resultant increases in longevity there has also been a gradual increase in ischemic CVD—a trend which is likely to become a worldwide phenomenon. For this reason, the development of techniques for the prevention and treatment of ischemic diseases of the brain is an issue of extreme importance for all of mankind.

Not only is normal brain function crucial to the individual, but it is worth emphasizing that the brains of world leaders play pivotal roles in current and future world events. The appearance of CVD, the concomitant loss of functions, and the decrease or complete halt in productivity thus have wide-ranging implications for the individual, for his family and for society at large. By the same token, the development of methods to prevent and treat this disease has importance not only for individual patients and their families, but also for the nations within which they work.

The essential nature of ischemic cerebrovascular disease can be described as necrosis of brain tissue due to decreased cerebral blood flow caused by stenosis or occlusion of cervical and/or intracranial arteries. Necrosis produces functional deficits in those parts of the brain and leads either to survival is an impaired condition or to death. While this pathology of CVD is, of course, common knowledge in medicine, it remains true that there is a considerable degree of uncertainty concerning the nature of the gradual intracerebral changes which occur following an ischemic attack. Among several fundamental questions which remain unanswered, the following should be mentioned: What level of reduction of cerebral blood flow and how prolonged a duration of occlusion will result in damage to brain tissue? What differences in these parameters exist in cases of focal ischemia and in cases of global ischemia? With regard to recirculation following ischemia, it must be said that, with the exception of morphological findings using the electron microscope, current research is little more than groping in the dark concerning neurophysiological and neurochemical results.

In the light of these uncertainties, it is evident that accurate evaluation of

the therapeutic effects of various drugs is simply not possible. Moreover, there are significant individual differences in the capacity for developing collateral pathways—a fact which makes evaluation of the prognosis following onset equally difficult. Due to further problems posed by changes in various components of circulating blood, age, blood pressure, associated disorders of the cardiac, pulmonary and respiratory systems, diabetes, and varying degrees of arteriosclerosis, it is evident that the effect of ischemia on brain cells is an extremely complex issue.

What kinds of medical therapy are currently in use for conditions of cerebral ischemia? First of all, with regard to prevention, gradually more favorable results have been obtained by means of dietary measures and the administration of drugs such as aspirin and wafarin to prevent arteriosclerosis and to prevent and/or treat hypertension.

Unfortunately, with regard to the therapeutic steps taken during the acute stage following the onset of ischemic CVD, whatever measures have been employed, the results have been little better than those following the natural course of the disease. Logically, it is easy to imagine that, by means of surgical treatment or the administration of hemolytic agents, vascular occlusions could be removed and efforts then made to increase cerebral blood flow. Such therapy, however, has been found to cause an increase in cerebral edema and cerebral hemorrhage, and for this reason attempts to induce vascular recirculation during the acute stage are now thought to be inappropriate. Surgical therapy is therefore also thought to be fruitless during the acute stage.

With regard to treatments currently in use for ischemic CVD, only two courses of action are open—neither of which is likely to lead to full recovery. Either the brain tissue which has been affected in the acute stage is considered beyond recovery and the patient is sent for rehabilitation with the neuronal deficits or, afternatively, by-pass surgery can be performed in order to allow for some slight recovery of the brain tissue in the penumbra of the focus.

Serious thought, as a matter of human compassion, should cirtainly be given to the problems of prevention of ischemic CVD and functional recovery through rehabilitation, but the most important questions concern the development of therapeutic techniques for the acute stage of the disease. Specifically, in order to prevent the rapid deterioration of the patient's cerebral condition and reduce the number of acute deaths, which are known to be a function of the interval from onset, it is essential to develop some form of therapy that can be to instituted as early as possible in the acute stage. That therapy, whatever it may be, would be of extreme importance and would constitute the first positive step forward in the treatment of ischemic cerebrovascular disease. During that period, while rapid deterioration of brain cells is being prevented, it would then be possible either to undertake vascular reconstruction or to allow for spontaneous increase in cerebral blood flow due to the emergence of collateral pathways.

The most difficult and frustrating task for the neurosurgeon is to be forced simply to observe the progression of cerebral infarction following onset and to be unable to take positive action. Similar to dealing with a house on fire, the most important step would be to take preventive measures at a very early stage in the event. From our own animal studies we have found that when cerebral flow is reduced to 40% of its normal level for a period of 3 hours, the morphology of brain cells is drastically changed and the cells are phagocytosed by leucocytes 24 hours later. Needless to say, despite the fact that there is total occlusion of capillaries and small vessels, leucocytes manage to destroy the infarctic brain tissue. Once the brain has entered such a condition, it is already too late to take therapeutic steps.

My own interest in and study of the ischemic brain began with an attempt to prolong the permissible time of temporary vascular occlusion for radical surgery on ruptured cerebral aneurysms—and indeed this quest has become a major lifework for me. At that time, an energetic young man, my classmate Akira Watanabe, entered the department of surgery of our college and began investigating hypothermic anesthesia in dogs. I turned my attention to the question of the permissible time for cerebral vascular occlusion using various degrees of hypothermia and soon learned how very difficult it is to reduce cerebral blood flow to zero. Eventually, I found that cerebral flow could be halted by means of throacotomy and occlusion of all the ascending arteries to the neck, but this experimental model proved to be extremely laborious!

Finding that 30 minutes of vascular occlusion could be done using hypothermic anesthesia at 27 °C, I performed my first aneurysm surgery using hypothermia on May 27th, 1961 and over the following years until 1969, I operated on many such cases. Considerable time however was needed for the lowering and subsequent raising of the patient's body temperature and, moreover, during that procedure complications such as cardiac arrest and skin burns were not uncommon. Throughout this period I pondered in the back of my mind whether or not there might be alternative means for prolonging the permissible occlusion time of cerebral vessels.

A fundamental turning point in our surgical technique came in 1969 when I experienced a case of ruptured cerebral aneurysm with severe cardiac complications. The anesthesiologist suggested that hypothermia alone would be fatal and since I had operated on some 300 aneurysm cases by then, I was confident that a successful operation could be done at normothermia. Craniotomy and dissection of the aneurysm were begun, but before actually reaching the aneurysm, there was a major re-rupture and intracerebral structures could no longer be distinguished or the aneurysm treated. Temporary occlusion of feeding and draining arteries of the aneurysm therefore became inevitable and the total occlusion time exceeded 50 minutes. Since cerebral necrosis occurs in about three minutes in medical common sense, there was no reason to expect favorable

results after such a prolonged occlusion. Expecting severe postoperative sequelae, I went to the patient's bed on the following morning and called her name. To my great surprise, we found her to be in a normal state of consciousness and to be without paresis.

My first thought was that this was surely a case of divine intervention, but the scientist in me soon returned and the entire staff was convened to examine what kinds of treatment the patient had received before, during and after the operation. At this point, I recalled that, in order to reduce the cerebral volume and enlarge the surgical field, 1,000 cc of 20% hypertonic mannitol solution had been administered by *i.v.* drip in such a manner that it was completed near the end of craniotomy. It was thus apparent that the mannitol may have been the factor which allowed for the prolonged occlusion of cerebral vessels without producing sequelae.

I asked Assistant Professor Takashi Yoshimoto, who was then a young M.D., if he would investigate the apparent capability of mannitol to suppress cerebral infarction, and in this way a long series of animal experiments were initiated. In order to clarify the effects of drugs such as mannitol, it was first necessary to establish an experimental animal model in which infarctic foci of the same size could be produced consistently at the same site in the brain. Furthermore, the severity of these foci would have to be controllable. Although research into the effects of mannitol was to begin with the development of such an ideal infarction model, animal models using various species and countless techniques did meet our expectations. Eventually, Dr. Yoshimoto went to Taiwan, where native Taiwanese monkeys were inexpensive enough to pursue such research to develop a model, but he returned despondent without success.

Upon hearing his bad news, I concluded that rigorous animal studies on the effects of drugs on brain infarction might in fact be impossible and I regretfully called a halt to the research project. But just two months after having abandoned hope, Dr. Yoshimoto strode into my office with four formalin-fixed dog brains in hand and announced: "I've done it!" When I asked what he had done, he proceeded to show me infarctic foci of similar size in the anterior thalamus of all four brains cut coronally through the optic chiasma.

As delighted as we both were, it was soon found that even when the four trunk arteries were visible when a unilateral temporal approach was used without doing damage of the temporal lobe, the incidence of anterior thalamic infarction was considerably lower than the initial indications of Dr. Yoshimoto's first four dogs. At that point, Dr. Tetsuya Sakamoto suggested that a deep electrode stereotaxically inserted into the anterior thalamus for the purpose of monitoring brain electrical activity would allow for confirmation of the infarction produced by means of occlusion of the four trunk arteries. It was then found experimentally that an ideal focus of infarction could be produced in virtually 100% of the animals using that technique. Subsequent work was then devoted to