THE EVALUATION OF BALLOON COMPRESSION METHOD IN SPINAL CORD INJURY MODEL STUDY TOWARDS NEUROLOGICAL ASPECT: CANINE CASE SERIES

RESEARCH PROPOSAL

Composed to Fulfil the Requirement Bachelor of Medicine Degree in
Faculty of Medicine, Public Health, and Nursing
Universitas Gadjah Mada

By:

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FACULTY OF MEDICINE, PUBLIC HEALTH, AND NURSING

UNIVERSITAS GADJAH MADA

YOGYAKARTA

2022

APPROVAL PAGE

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Had been examined and approved at

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CHAPTER I
INTRODUCTION

A. Background

Spinal Cord Injury (SCI) is a traumatic event that has a devastating effect in neurological deficit, such as irreversible sensory, motor, and autonomic nerve disability below the level injury (Han *et al.*, 2018). Globally, traumatic SCI affects 250.000-500.000 persons with insignificant recovery in those severe injuries (WHO, 2017). Up to now, there is no definite treatment for SCI (Nakamoto *et al.*, 2021), therefore various treatment strategies have been developed among researchers to improve patients' quality of life. Performing human clinical trials is ineffective because it is expensive and time consuming.

Reproducible, submaximal yet sufficient spinal cord injury model is needed to perform preclinical experimental study for development of therapeutic techniques and prediction of clinical outcome to be conducted (Lim *et al.*, 2017). Animal models are primarily used for SCI studies considering inaccessibility to human patients and supported by its similarities to human's anatomical structure (Yu *et al.*, 2012). Choosing the most suitable animal models is challenging due to its lack of familiarity with the model among nonveterinary scientists, moreover, how and where the translational process of the animal model would be most valuable is still questionable.

In recent years, the use of canine for spinal cord injury is a rapidly evolving field in experimental study, and it is proven that the canine model of SCI parallels the human condition with respect to patient and lesion heterogeneity, clinical management, available outcome assessment tools and spinal cord histopathology. Canine is proven to enhance translation from benchtop to human besides with the overall goal being to improve functional outcome for persons and animals affected by SCI(Moore *et al.*, 2017).

There are several methods to choose for SCI simulation that are developed based on injury mechanism, specifications, and relevance to human SCI. It is crucial to pick the right models, a few methods relatively easy to reproduce but less relevant to human SCI. Complicated device setup, inconsistency, and impact parameters not recordable are the main threat of choosing the suitable methods for SCI. According to those obstacles, the compression and contusion models are considered to be the most relevant and commonly employed methods followed by its convenience to understand the secondary injury mechanism and therapeutic development for SCI (Alizadeh, Dyck and Karimi-Abdolrezaee, 2019).

Therefore, this observational study will evaluate and describe the simulation of SCI using balloon compression methods through inflation of Fogarty® catheter using canine that can be translated to humans.

B. Problem Formulation

According to the study background and limitations of research in Indonesia that discuss this topic, therefore the problem formulation which will be discussed is how is the evaluation of balloon compression method in spinal cord injury model study towards neurological aspect in canine.

C. Study Objective

1. General objectives:
    1.1. This study was intended to evaluate the balloon compression method in spinal cord injury model study towards neurological aspects in canine.
    1.2. To improve knowledge on SCI pathological mechanism that in the future can be used for treatment strategies relies on animal model
2. Specific objectives:
    2.2. To know the proper animal model with proper method in SCI simulation
    2.3. To investigate the pattern of neurological impairment in SCI due to induction of SCI by balloon compression
    2.4. To know the factors that influence the process of SCI simulation in canine

D. Research Benefits

1. **Academic**

This study was conducted to increase the author's knowledge and understanding regarding the evaluation of balloon compression method in spinal cord injury model study towards neurological aspect in canine. This research was also conducted to fulfill the author's educational requirements in obtaining a Bachelor of Medicine degree, Gadjah Mada University.

2. **Community**

The results of this study are expected to provide information about the evaluation of balloon compression method in spinal cord injury model study towards neurological aspects in canine, both from the general public, health workers, academics, and educational institutions, and results are expected to encourage further research about spinal cord injury treatment. Results of this case series can be used to generate hypotheses that are useful in designing further studies, including randomized controlled trials.

E. Study Originality

No.	Study Title	Design and Method	Result	Difference
1.	Development of an improved canine model of	Animal experimental study was conducted to do a minimally invasive canine	All seven dogs showed complete paraplegia after	Motor function was scored by Tarlov scoring

	percutaneous spinal cord compression injury by balloon catheter (Lee *et al.*, 2008)	model of spinal cord injury (SCI) by balloon catheter compression that inserted into the epidural space via the lumbosacral space, and inflated between L2 and L3 for 30 or 60 min under fluoroscopic guidance. Motor function after SCI was assessed using modified Tarlov scale.	the procedure, neurological problems were evident and the modified Tarlov scores remained at zero after the procedure; no improvement in clinical signs was observed.	method. Balloon compression performed between L2 and L3
2.	Technique of Spinal Cord Compression Induced by Inflation of Epidural Balloon Catheter in Rabbits (Oryctologus cuniculus): Efficient and Easy to Use Model (Antonio *et al*., 2016)	Animal study was conducted using 60 rabbits by dorsal laminectomy technique that was carried out between the vertebrae L2 and L4, and removing the dorsal spinosus processes of L3, where the Fogarty® catheter slowly and dorsal to the spinal cord was introduced until the height of the T13 vertebra, then using air to inflate the balloon that remained for ten minutes.	Balloon compression model was able to reproduce acute spinal cord injury since all the animals being clinically evaluated showed sensory, motor and autonomic losses.	The animal model was using rabbit.
3.	New Model of Ventral Spinal Cord Lesion	Experimental study was conducted by performing ventral compression of the	The compression resulted in severe	The experiment

	Induced by Balloon Compression in Rats (Krupa *et al.*, 2020)	SCI by the anterior epidural placement of the balloon of a 2F Fogarty's catheter, via laminectomy, at the level of T10. The severity of the lesion was assessed by behavioral and immunohistochemical tests.	motor and sensory deficits.	was conducted in a rat model.

Table 1. Study Originality

CHAPTER II

A. Literature Review

1. Anatomy of spinal cord

Spinal cord is located within the spinal canal of the vertebral column that covered by cerebrospinal fluid and meninges. The human spinal cord can be subdivided into 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and coccygeal part with a total 31 segments. Each segment consisting a pair of dorsal and ventral roots originates, that are composed of individual dorsal and ventral rootlets, which exit together to spinal cord at the corresponding anterolateral and posterolateral depression, respectively. The rute of spinal roots is descending further down and go through the exit column at the appropriate intervertebral foramen (rostral for C1-C7 roots, caudal for all other). The spinal cord gives rise to a series of spinal nerves on either side. There are a swelling called dorsal nerve root ganglion (spinal ganglion) that relies on dorsal root. This spinal ganglion contains cell bodies of pseudounipolar sensory neurons. The vertebral column and spinal cord's development is different, that makes spinal segments do not lie opposite their corresponding vertebrae. It is important to know that the length and obliquity of the spinal nerves increase progressively caudally before their exit throught the intervertebral foramina, because it is plays role in laminectomy to relieve spinal cord compression due to traumas.

In a transverse section of the spinal cord, two distinct area can be seen with the naked eyes, called an inner grey matter consisting the collection of cell bodies of neurons, and an outer white matter, collecting the fibers that running through the spinal cord or a place for spinal tracts.

Spinal tracts divided into two types – ascending and descending tracts, that each tract have its own function. The descending tracks are mainly for motor function and ascending tracks are mainly for sensory function (Khan and Lui, 2021).

Spinal tract begin with the cortico-spinal tract that are mainly from the motor area of the cerebral cortex (area 4) with some contribution from the premotor area (area 6), somatosensory area (area 3, 2, 1) and parietal cortex (area 5). The internal capsule posterior limb contains fibers occupy the middle part of the midbrain's crus cerebri. The tracts then go through the ventral part of the pons and descends through the pyramids in the medulla. By the end of the medulla, approximately 80% of the fibers cross to the opposite side of the spinal cord, called the pyramidal motor decussation. After these fibers crossed, they will enter the lateral funiculus of the spinal cord and continue as the lateral corticospinal tract. Synapse of fibers and internuncial neurons of dorsal and ventral columns is the end of the tract that located at various levels of spinal cord's grey matter. The rest of 20% of the uncrossed corticospinal tract fibers will descend within the anterior funiculus as the anterior corticospinal tract. In such a way, all fibers of the corticospinal tract eventually cross to the opposite side and

connect the cerebral cortex of one side with the ventral horn cells of the opposite part of the spinal cord. Therefore, these fibers are called upper motor neurons, while the fibers that begin in the ventral horn cells and descending downwards will be called lower motor neurons (Khan and Lui, 2021).

2. Spinal cord injury

Spinal cord injury (SCI) is a devastating traumatic event that resulting irreversible sensory, motor, and autonomic nerve disability below the level injury (Han et al., 2018). Each year, around 250,000 – 500,000 patients globally suffer from spinal cord injury that mostly occurs from traffic accidents (WHO, 2017). Over the last decade, the clinical management and survival rates following spine injury are start to improved, however there is no curative and definite interventions that are currently available despite all of the on going research which aim the restoration of loss tissues and development of neurological function (Nakamoto *et al.*, 2021). Generally, SCI occurs due to either direct trauma to the spinal cord or from compression due to fractured vertebrae or even caused by epidural hematomas or abscesses (Bennett, M Das and Emmady, 2022).

Pathophysiology of SCI consist of a cascade, such as primary injury and secondary injury. Primary injury of SCI results from a direct physical and mechanical forces that acting on the spine in various position, such as flexion, extension, rotation, distraction, compression, or a mixture of them (Weidner, Rupp and Tansey, 2017). These primary damages affecting a

mechanical disruption of axons and other membranes of neural and glial cells and also in damage of blood vessels and hemorrhages within the gray matter. The damage of the axon, affecting the segment below the level of injury that can manifest as either complete functional loss or incomplete lesion (Kalkulas, 1999).

In secondary injury, a cascade of events start within a minutes and continue for weeks or months following the initial primary injury that includes acute phase consisting vascular damage, ionic imbalances, free-raducal formation, the initial inflammatory response, and neurotransmitter accumulation. In the subacute phase, demyelination of surviving axons, Wallerian degeneration, matrix remodeling, and formation of the glial scar started to begins (Alizadeh, *et al*., 2019).

Early acute phase occurs in 2-48 h post-injury and during this phase, hemorrhage is still on going followed by severe edema and inflammation. Necrosis due to acute cell death thought to be uncontrollable. Secondary damage processes started to induce that may provoke the additional axonal injury, cell death, and the propagation of the lesion within the surrounding spared tissue (Profyris *et al.*, 2004).

Subacute phase begin at day 2 post injury that is characterized by the continuation of an intensive phagocytosis in the lesion site targeting accumulated cellular debris (Donnelly and Popovich, 2008). The fibroglial scar started to formed that consists of extracellular matrix (ECM) and various cells which developing in and around the lesion (Khan and Lui,

2022). In the transitional phase between subacute to chronic, maturation of the astrocytic scar and regenerative axonal sprouting are can be seen (Hill, Beattie and Bresnahan, 2001). After many years, Wallerian degenerative will remains active to aiming the removal of severed axons and the respective cell bodies, therefore 1 – 2 years are needed for the lesion and the associated functional deficits to stabilized (Weidner, Rupp and Tansey, 2017).

3. Balloon compression

The experimental study of spinal cord injury has been created by various methods, a few surgical procedure to induce SCI require surgical exposure of the spinal cord and lesion induction by using a sharp instrument or a device that provides static or dynamic compression (Seth *et al.*, 2018). Compressive models of SCI have been used for several decades, differ from contusion model that achieved by applying a force for a very brief period, the compression models consists of an initial contusion for milliseconds followed by a prolonged compression through force application for a longer duration (seconds to minutes) (Alizadeh, Dyck and Karimi-Abdolrezaee, 2019). For a larger animals such as dogs and cats, balloon compression model has been used in consideration of easy to perform (Aslan, 2009).

The procedure of ballon compression is used by inserting a catheter with an inflatable balloon to a epidural or subdural space. To create the force for induction of SCI, the balloon will undergo inflation with air or saline for a specific duration of time (Cheriyan, 2014).

4. Animal models

Experimental study for SCI treatment strategy has been developed over the years. Performing the clinical trials on humans requires high cost and time consuming. Key challenges in developing therapeutic strategies for SCI are the translation from animal to human, thus robust models of injury that mimic human condition are needed. Rodents are the most common animal models in laboratory science, however those evaluated in human clinical trials do not show an unequivocal improvement. In contrast, dogs that are classified as canine, have proven useful in pioneering and rigorously testing several treatments that successfully translated into human clinical practice, such as Addison's disease, retinal degeneration, and malignant glioma (Chase *et al.*, 2006). This discovery makes canine have a potential to screen new interventions for people with SCI.

In recent years, using canine as animal models of SCI has gone through several consideration and has been identified by potential strengths, includes natural history of injury can be identified, that is shared by pathological aspects with certain human SCI cases, in a population of animals with various diverse genetic, health comorbidities, and other confounding clinical factors that are encountered in human clinical trials. Physical size and metabolism of canine provides "scaling up" for therapeutics for human trials. A failure to recover after an acute injury in canine, making them available for study of interventions aimed at chronic

SCI that have been identified as a research priority by the human SCI community, since the laboratory studies of chronic injury are logistically challenging and requires high cost (van Middendorp *et al.*, 2016).

Canine model of SCI parallels the human condition in aspect of lesion heterogeneity, clinical management, available outcome assessment tools, and spinal cord histopathology (Moore, 2017).

5. Neurological aspect

Neurological aspect in this study consists of sensory, motor, and reflex function that will be asses with different method for each aspect. Sensory function is checked by how long canine will response to a hot and cold stimulus or termed thermal sensory testing (Gorney *et al.*, 2016).

While motor function will be checked by cBBB scoring and reflex function can be done by checking the deep tendon reflexes (DTR) of the limb. The deep tendon reflex (DTR) are crucial to determine the upper or lower motor neuron lesion, which can be seen in the presence of hyporeflexia or hyperreflexia. National Institute of Neurological Disorders and Stroke (NINDS) provide a grade for DTR that ranges from:

- 0: Absent reflex, no reaction
- 1: Small reflex, less than normal, or obtained with reinforcement
- 2: Lower half of normal reflex
- 3: Upper half of normal reflex

- 4: Increased reflex. Clonus may be present, and it is always pathological

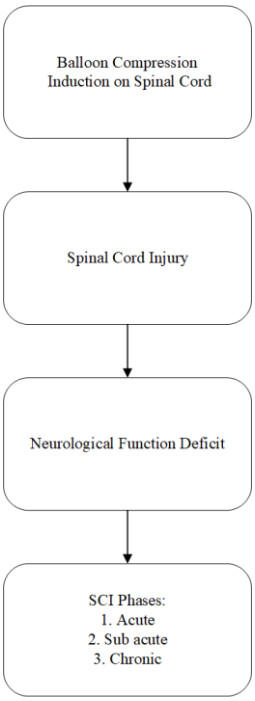
(Rodriguez-Beato and De Jesus, 2022)

Adaption of Basso Beattie Bresnahan (BBB) scale are used in a clinical dog model of acute thoracolumbar SCI. Modification of BBB scale aim to account for species differences in locomotion. The new modification of this scale is called canine BBB scale (cBBB). This scale assess the canine paw and tail position, and trunk stability that ranged from 0 – 19 point scale.

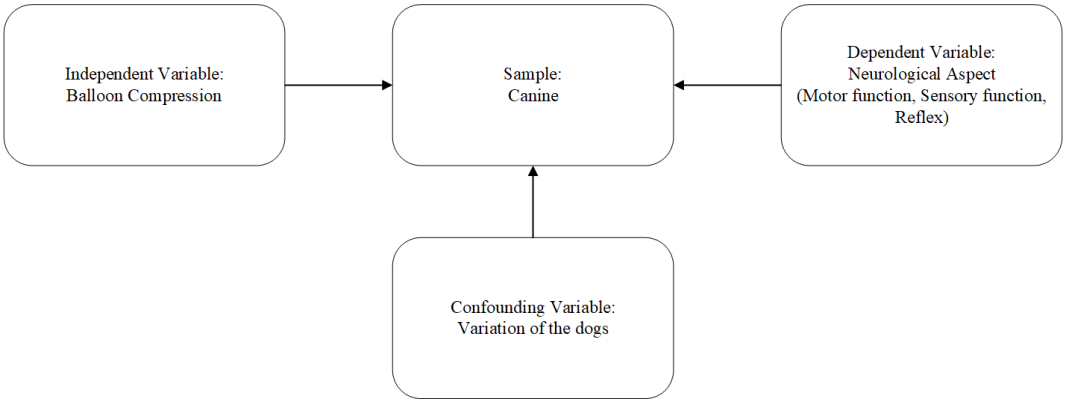
Score	Description
0	No observable hind limb (HL) movement
1	Slight movement of one or two joints
2	Extensive movement of one joint, or extensive movement of one joint and slight movement of one other joint
3	Extensive movement of two joints
4	Slight movement of all three joints of the HL
5	Slight movement of two joints and extensive movement of the third
6	Extensive movement of two joints and slight movement of the third
7	Extensive movement of all three joints in the HL
8	Plantar placement of the paw with no weight support
9	Plantar placement of the paw with weight support only when stationary, or occasional, frequent or consistent weight-supported dorsal stepping and no plantar stepping
10	Occasional weight-supported plantar steps; no FL–HL coordination
11	Frequent to consistent weight-supported plantar steps *and* no FL–HL coordination
12	Frequent to consistent weight-supported plantar steps *and* occasional FL–HL coordination
13	Frequent to consistent weight-supported plantar steps *and* frequent FL–HL coordination
14	Consistent weight-supported plantar steps, consistent FL–HL coordination, *and* predominant paw position is *externally rotated* when it makes initial contact as well as just before it is lifted off; or frequent plantar stepping, consistent FL–HL coordination, and occasional dorsal stepping
15	Consistent plantar stepping and consistent FL–HL coordination and *no toe clearance* or *occasional* toe clearance; predominant paw position is *parallel* to the body or *internally rotated* at initial contact
16	Consistent plantar stepping and consistent FL–HL coordination and toe clearance occurs *frequently*; predominant paw position is parallel or internally rotated at initial contact and *externally rotated* at liftoff
17	Consistent plantar stepping and consistent FL–HL coordination and toe clearance occurs *frequently*; predominant paw position is *parallel* or *internal* at initial contact and at liftoff
18	Consistent plantar stepping and consistent FL–HL coordination and toe clearance occurs *consistently*; predominant paw position is parallel or internal at initial contact and at liftoff. *Trunk instability is present*
19	Consistent plantar stepping and consistent FL–HL coordination and toe clearance occurs consistently during forward limb advancement; predominant paw position is parallel or internal at initial contact and at liftoff. *Trunk instability is not observed*

Figure 1. BBB score (Basso, Beattie and Bresnahan, 1995)

B. Theoretical Framework



C. Conceptual Framework



CHAPTER III

RESEARCH METHOD

A. Study Design

This is a case series study in observational research design and it's a part of larger experimental research.

Procedure:

1. Balloon compression insertion

Male dogs were used as an experimental model. The weight of the animals undergoing surgery was 10-15 kilograms. All the surgery was performed in a specialized operating room for animals (Prof. Soeparwi Animal Hospital). At the beginning of the procedure, the animals were prone positioned and fixated on the bed thus the area that will be given induction is the dorsal area. General anesthesia was introduced by a face mask with isoflurane 1-2% 250mL that inhaled along with oxygen during the procedure. The back of the animal was shaved and the skin cleaned with disinfectant. Under sterile conditions, marked the area in L1 of the vertebra. Skin and connective tissue were given incision in the dorsal area. Then, incision of m. paraspinal is done. After L1 was identified, ligamentum supraspinal and ligamentum interspinosus were excised to get the field of view of ligamentum flavum. Perform a perforation of the ligamentum flavum using a rongeur

forceps. Adjust the size of perforation so the catheter can be inserted to the spatium epidural of canalis vertebralis. Insert the fogarty catheter through ligamentul flavum. Place the catheter from caudal to rostral until reach T10-T11 segment of spinal cord. Observe the position of catheter using C-arm, and do a correction if the position of the catheter is not at T10-T11 segment. Inflate the balloon by iohexol contrast gradually for 2 minutes. Once the balloon catheter finished to inflate completely and filling the epidural space, make sure the balloon already compressed the spinal cord. Control bleeding if needed. Balloon compression is maintained for 6 hours. Do the suturing until operation area are closed. After 6 hours, take out the catheter without opening the sutures. Give post operation therapy of gentamicin 80.000 unit intramuscularly for 5 days.

2. Post operation observation

- Motor

  Canine is placed in a 3 m x 3,5 m room and are expected to move freely, if it does not have the desire to move, it will be provoked verbally to move. Observation will be recorded for 4 minutes in an observation day until it euthanized. Then the video will be scored by cBBB scoring.

- Sensory

Thermal sensory testing was done by using both hot and cold stimuli in 49°C (for heat) and 5°C (for cold) using a stainless steel stick as the medium between the ice and fire to the skin of the canine. The stick will be placed in three points of hind limb such as proximal, medial, and distal. During each location of the testing, the stick was held in a place until the canine showed a behavioral response, indicating conscious perception of the stimulus or the maximum amount of time had been reached. The maximum times were 30 and 60 seconds for hot and cold, respectively. This procedure should also be recorded with a camera.

- Reflex

  Canine should be positioned in lateral recumbency, with the hind limb in a flexion condition. Do the examination with hammer in the patella. Observe the movement of patella and classified the grade into hyperreflex, hyporeflexia, or normoreflex.

B. Study Time and Setting

Time : September 2021 – February 2022

Setting : Prof. Soeparwi Animal Hospital

C. Study population

Inclusion criteria:

1- 2 years male dog weighted 10-15 kilograms

Exclusion Criteria:

Dog with active infection, neurological and musculoskeletal disorder, or having another pathological disorder

Sample Size:

This is a case series study with a sample size of 3 dogs with inclusion and exclusion criteria that are already mentioned above.

D. Data collection tools

The collected data by observation of the sample in the setting will be explained in descriptive method.

E. Study variable

Independent variable:

Balloon compression on spinal cord of canine model

Dependent variable:

Neurological aspect of canine model

F. Operational definition

Variable	**Definition**
Spinal Cord Injury (SCI)	Spinal cord injury is damage to the spine, specifically to the tight bundle of cells and nerves that sends and receives signals

	from the brain to and from the rest of the body below the level of injury and often caused by direct injury to the spinal cord.
Balloon compression	Balloon compression model is a procedure to induce SCI by a catheter with an inflatable balloon that is inserted in the epidural or subdural space followed by inflation of the balloon with air or saline for a specific duration of time provides the force.
Canine model	A model of experimental study that used dogs as a subject.
Neurological aspect	An aspect in neurology that consist of sensory function, motor function, and reflex.

G. Study Plan

The study plan of this study are as follows:

1. Preparation phase
   - Collecting the reference and composing the research proposal
   - Present the proposal to the advisor in proposal seminar session
   - Administration of the ethical clearance to the Ethical Committee of FK-KMK Gadjah Mada University
2. Implementation phase
   - Data collection by observation to the sample that fulfil the inclusion and exclusion criteria and already given intervention in Prof. Soeparwi Animal Hospital for a certain time

3. Reporting phase

   Reporting the result of observation in a case series, then arranging the discussion, conclusion and acknowledgement based on the study findings.

H. Stasticial Analysis

This study will be provided in descriptive form of a case series.

I. Ethical Consideration

The data used in this study is obtained from a larger study with a title “Aplikasi Kombinasi Antara Sel Punca Alogenik Dan Perancah Medula Spinalis Yang Terbuat Dari Serat Berukuran Nano Melalui Proses Elektrospinning Pada Kasus Cedera Tulang Belakang Di Hewan Coba” with the main researcher dr. Yudha Mathan Sakti, Sp.OT(K) therefore the ethical clearance has been given.

J. Study Timeline

2022								
Activity	May	June	July	Aug	Sept	Oct	Nov	Dec
Writing and Revision of Proposal Research								
Title Application								

Seminar of Research Proposal								
EC Submission of Research Proposal								
Data Collection and Analysis								
Writing of Research Result								
Seminar of Research Result								
Revision of Research								
Final Examination								
Publication								

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