Role of Steroid in the Treatment of Chronic Subdural Haematoma

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DECLARATION

I hereby humbly declare that this thesis entitled **"Role of steroid in the treatment of chronic subdural haematoma"** is based on work carried out by me and no part of it has been presented previously to any Academic Institute or University for any higher degree.

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CERTIFICATE

This thesis titled **"Role of steroid in the treatment of chronic subdural haematoma"** Submitted by **Md. Abdus Salam** in the Department of Clinical Pharmacy and Pharmacology, University of Dhaka in fulfillment of the requirement for the degree of Doctor of Philosophy. No part of the work has been submitted for another degree or qualification in any other Institution.

Supervisor

Professor Dr. Md. Saiful Islam

LIST OF ABBREVIATION & ACRONYMS

ACE	Angiotensin Converting-Enzyme
aPTT	Activated Partial Thromboblastin Time
BHC	Burr Hole Drainage
CSD	Closed System Drainage
CSDH	Chronic Subdural Haematoma
CSH	Chronic Subdural Haematoma
CT	Computed Tomography
DMCH	Dhaka Medical College Hospital
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
INR	International Normalized Ratio
MGS	Markwalder's Grading Score
MRI	Magnetic Resonance Imaging
SD	Standard Deviation
SPSS	Statistical Package For Social Sciences
TDC	Twist Drill Craniostomy
VEGF	Vascular Endothelial Growth Factor
Cox-2:	Cyclooxygenase 2
CSF:	Cerebrospinal Fluid
mRS:	Modified Rankin Scale
GOSE	Glasgow Outcome Scale Extented
IL	Interleukin
PGE2	Prostaglandin E2
t-PA	Tissue Plasminogen Activator
ACTH	Adrenocorticotropic Hormone
HAT	Histone Acetyktransferase
TBP	TATA box Binding Protein
GM-CSF	Granulocyte –Macrophage Colony Stimulating Factor
NCoR	Nuclear Receptor Corepressor

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Abstract

Chronic subdural haematoma (CSDH) is a frequent neurological pathologic entities in daily neurosurgical practice with a rapidly rising incidence due to increasing age & wide spread use of anticoagulant. The "gold standard" of treatment is surgical evacuation by burr-hole craniostomy (BHC) for symptomatic patients but associated with complications, a recurrence rate of up to 30%, 1-year mortality rates could be as high as 32%. A complex intertwined pathway of inflammatory process, angiogenesis, local coagulopathy, recurrent microbleeds & exudates play a major role in the pathogenesis of CHDH. The objective of this study showed the effect of primary DXM therapy in treating CSDH is safe, beneficial, promising functional outcome & cost effectiveness as an alternative to BHC & surgical drainage in selected group of patients

This study is a prospective, single centre, open labeled, randomized controlled clinical trial (RCT). Consecutive patients with a CSDH with MGS grade 1-3 will be randomized to treatment with DXM therapy or BHC. The DXM protocol will be 4 mg 8 hourly either oral or i/v for 21 days, which is then slowly tapered 1 mg per day every 3 days for 4 weeks.For insufficient haematoma resolution BHC can be performed.The primary outcomes are the functional outcome by means of the mRS score at 3 months & cost effectiveness at 12 months.Secondary outcomes are QOL at 3&12 months using the SF-36 & QOL/BRI, haematoma thickness after 2 weeks on follow-up CT, haematoma recurrence during the first 12 months,complications & drug related adverse effects,failure of therapy within 12 months after randomization & intervention,mortality during first 3&12 months,duration of hospital stay & overall healthcare & productivity costs. To test non-inferiority of DXM therapy Vs BHC,finally 30 patients in DXM therapy arm & 30 patients in BHC arm are required.

The study started in June 2012; its outcomes demonstrates interesting alternatives to BHC in the management of patients harboring CSDH.

Based on pathophysiologic mechanisms & patient studies treatment with steroid play a major role in the treatment of CSDH & as effective as BHC on functional outcome,at lower costs.

Introduction

Neurosurgeons are familiar with chronic subdural haematoma, a well-known clinical entity, which is usually treated by some modality of trepanation. Despite the excellent outcomes obtained by surgery, complications may occur, some of which may be potentially severe or fatal. Furthermore, up to 30% recurrence rate is reported.I want to present a noble approach for the management of CSDH based on the use of dexamethasone as the treatment of choice in the majority of cases.[1]

Chronic subdural haematoma is a well-defined clinical condition consisting in a slowly progressive accumulation of liquefied blood within the subdural space. Such collection may, eventually, produce hemisphere compression and result in ultimate brain herniation. It is diagnosed in 5 persons in every 100000 in the general population per year.[2,3]

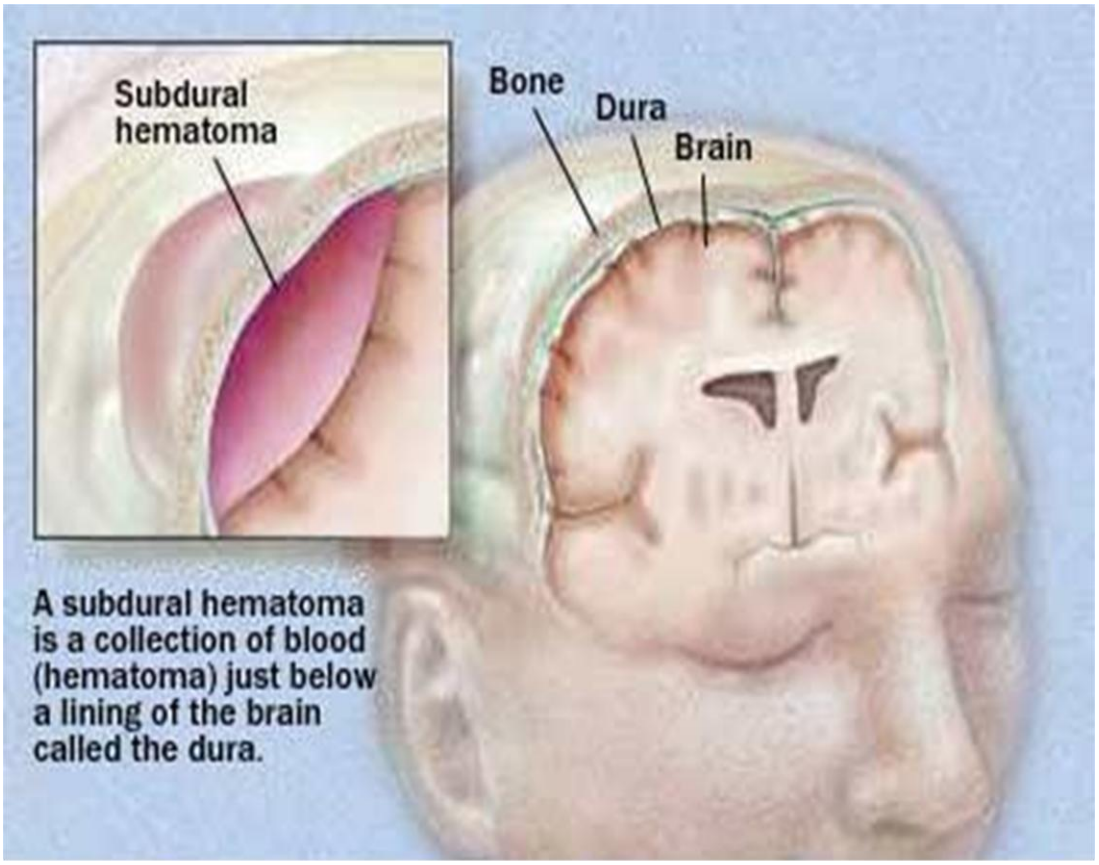


Fig 1: Subdural Hematoma

The incidence is higher in the elderly (up to 58 per 100000 in people older than seventy), and in patients with a history of alcohol abuse or coagulation disturbance.[4] Minor head trauma a few weeks before presentation is a common antecedent. Slow venous bleeding and the creation of neo-membranes around the subdural clot are some recognized pathogenic features in the development of CSDH.[4] Neurosurgeons around the globe are familiar with this condition and many of them consider symptomatic CSDH a clinical scenario that requires prompt specialized evaluation and neurosurgical intervention, often on an emergency basis. At present, burr-hole or twist-drill craniostomy and drainage are the most widely used surgical techniques.[5] Neurological outcome after surgical evacuation of CSDH is known to be remarkably favourable in the great majority of patients.[6,7] Nevertheless, wound infection, subdural empyema, tension pneumocephalus, brain contusion, subdural or epidural haematoma, intracerebral haemorrhage, catheter penetration of the brain,RTI,UTI and even death may occur after surgery.[6] Additionally, up to 30% of patients need to be re-operated on due to re-accumulation of blood.[2] Surprisingly, despite this tendency towards recurrence and its related morbidity, prognosis in CSDH seems to be more influenced by the age of the patient and his/her presenting neurological status than by the type of intervention performed.[8] Thus, for adequate evaluation and analysis of outcome, it is appropriate to classify patients according to functional clinical scales such as Markwalder's grading score (MGS).[9] Nonoperative measures, such as, hypertonic or hyperosmolar solutions and systemic glucocorticoids have been used in CSDH with favourable results .[3]

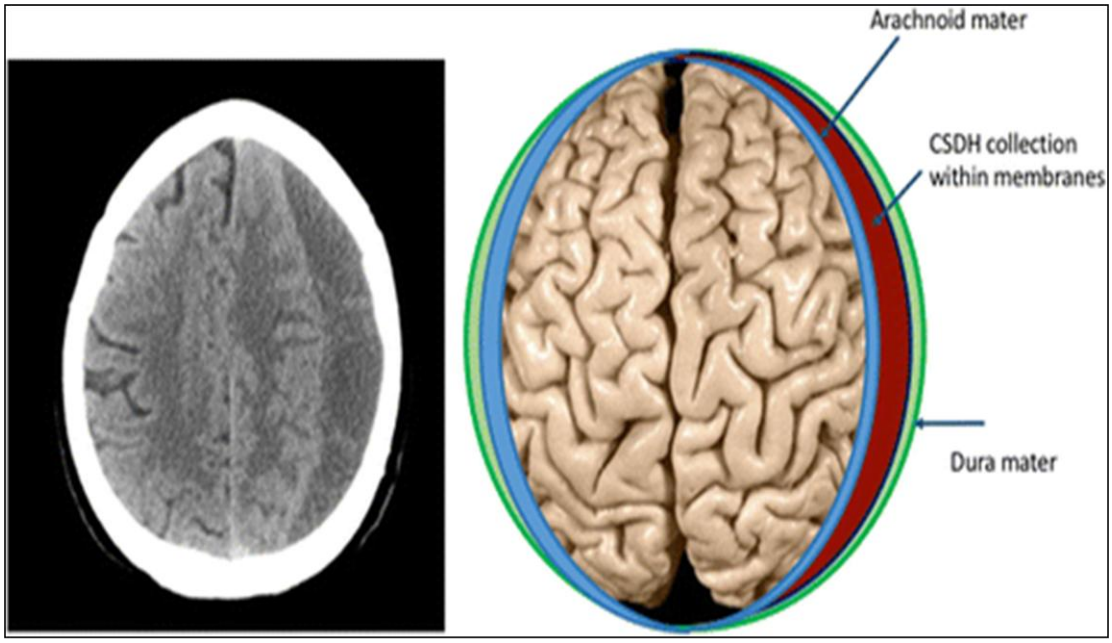


Fig 2: CSDH collection within membranes

Noticeably, the literature concerning these therapies consists of small case series and very few clinical observations.[10] Thanks to a widespread availability of modern neuroimaging, many cases of CSDH with few or no symptoms at all are incidentally found. Although the overall morbidity and mortality associated with surgical drainage are low, it seems reasonable to offer less aggressive measures, at least, to this subset of patients. Successful resolution of CSDH either spontaneously or after medical treatment has been reported before, even for severely impaired patients.[3] Nevertheless, recommendations favoring non-operative treatment of CSDH are supported by scarce literature. The natural history of untreated or medically managed CSDH is not well known. In fact, very few papers discuss on the advantages and disadvantages of surgical versus medical therapy and, virtually none of them compare the outcomes and morbidity-mortality in a well-designed clinical trial. Systemic steroid therapy has been used in CSDH as an alternative to surgical evacuation in selected patients. The rationale for its use lies on the complex effects of corticoids over the clot membrane and neovascularization.[11]

Chronic subdural haematoma is an encapsulated collection of old blood between the dura mater and subarachnoid caused by tear of bridging veins. Repeated bleeding from external membrane capillaries facilitated by fibrin degradation products leads to its expansion7. CSDH is fairly common disease, especially in the elderly with incidence ranging between 1.73 to 13.18 per 100,000 population. This population is

also likely to have other associated comorbidities that can impact on immediate postoperative outcome and overall survival.

Known risk factors for chronic subdural haematoma include coagulopathy, alcoholism, trauma and low intracranial pressures for example after lumbar drainage or ventricular peritoneal shunt. Clinical presentation is varied but patient commonly presents with headaches, confusion, drowsiness, vomiting, seizures, ataxia among other presentations and on examination, patient have various neurological deficits including a low Glasgow coma scale, ophthalmoplegia, hemi paresis/hemiplegia among other deficits.

Diagnosis is confirmed by non contrast CT scan head as study of choice although in some instances MRI may be indicated. The imaging pattern has a direct influence on post operative outcome especially in terms of recurrence.25

Management of this condition can either be conservative with use of low dose steroids or surgery. Surgical options are still controversial with no level I evidence for standard modality although burr hole craniostomy (BHC) is initially recommended due its high safety-effectiveness ratio. BHC with CSD (closed system drainage) has marginal benefit over BHC with irrigation in terms of recurrence and hospital stay according to some studies44. However the latter is most cost effective, making it ideal in our resource constrained setup.

Rationale of the Study

The rationale for the use of dexamethasone in CSDH lies in its anti-angiogenic properties over the subdural clot membrane, impede the formation of neomembrans & neocapillaries by their powerful inhibition of inflammatory mediators such as lymphokins, PG & stimulation of inflammatory inhibitors like lipocortin. Dexamethasone induce the secretion of the inhibitor of plasminogen, a substance that reduces the cycle rebleeding – lysis of the clot & reduce the expression of VEGF which inhibits abnormal angiogenesis. Dexamethasone is a feasible treatment that positively compares to surgical drain. It avoided two thirds of operations. The natural history of CSDH allows a 48-72 hours dexamethasone trial-

Without putting the patient at risk of irreversible deterioration:

Eliminates all morbidity related to surgery & recurrences.

Does not provoke significant morbidity itself.

Reduces hospital stay.

Does not preclude ulterior surgical procedures.

It is well tolarated & understood by the patient & relatives.

Reduces cost.

So we propose a protocol that does not intend to substitute surgery but offer a safe & effective alternative. Although few studies has been done in this topic globally. No such study in Bangladesh has been documented. More over this study will provide scenario of the outcomes of role of steroid in the treatment of CSDH in a tertiary hospital of Bangladesh which may be a future reference for further study and improve the outcome & will be helpful in framing the national strategy.

Objectives

To evaluate the effect of management of CSDH after treatment with steroid.

To test the necessity of steroid as non-surgical alternative in the management of CSDH.

To assess the morbidity and mortality of CSDH following steroid management.

To compare the functional outcome of the management of CSDH with or without steroid drugs.

To evaluate the recovery, QOL & cost effectiveness of the patients of CSDH with or without steroid drugs.

Literature Review

Subdural haematoma is bleeding or a collection of blood between the dura mater and arachnoid of the brain usually as a result of a tear in the bridging veins that cross this space. It can be classified into acute, chronic, and subacute. Acute refers to symptoms which manifest before 48 hours post injury, subacute are those manifesting between 48 hours and 2 weeks, whilst chronic to those manifesting after 2 weeks.[12]

Acute refers to symptoms which manifest before 48 hours post injury, subacute are those manifesting between 48 hours and 2 weeks, whilst chronic to those manifesting after 2 weeks.[6] Acute cases usually present immediately after trauma and often the victim is unconscious. However, CSDH may present in the elderly or alcoholic patients with vague complaints or change in mental status.[13]

Virchow first described it in 1857 as "pachymeningitis hemorrhagica intema". Later[8] Trotter put forward the theory of trauma the bridging veins as a cause of what he named "Subdural Hemorrhagic Cyst". Since then trauma has been recognized as an important factor in the development of CSDH.

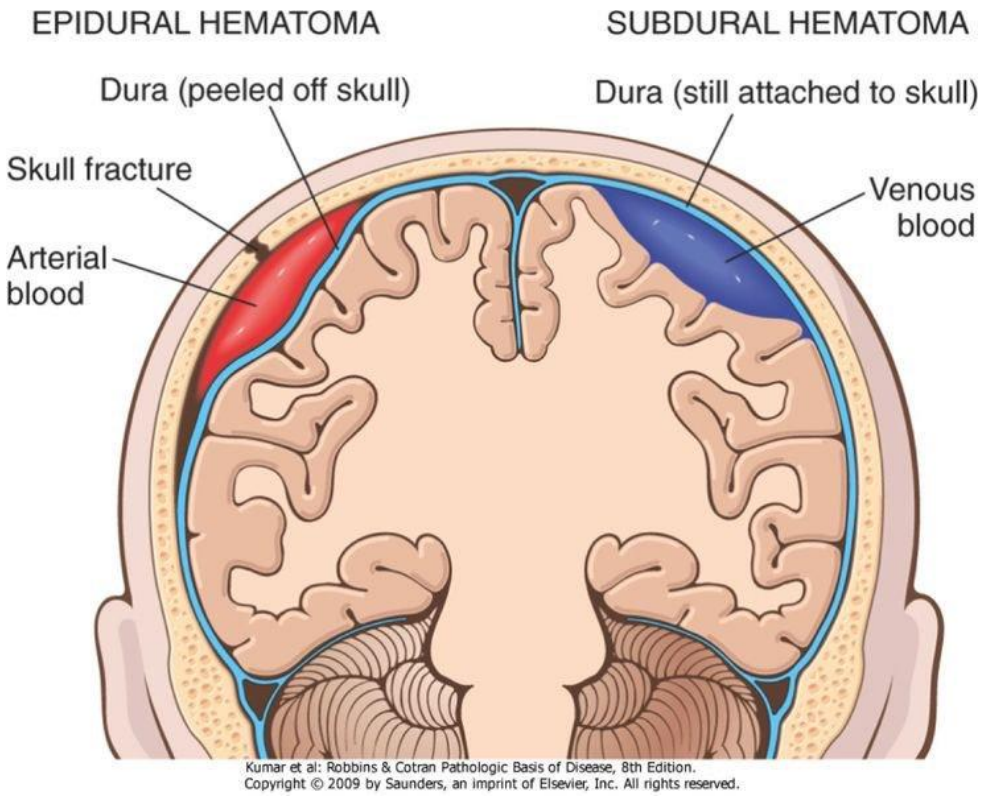


Fig 3: Epidural & Subdural Hematoma

CSDH is commonly associated with cerebral atrophy. The cortical bridging veins are thought to be under greater tension as the brain gradually shrinks from the skull, even minor trauma may cause one of these veins to tear. Slow bleeding from the low - pressure venous system often enables large haematomas to form before clinical signs appear. Small subdural haematomas often resorb spontaneously. Large collections of subdural blood usually organizeand form vascular membranes that encapsulate the subdural haematoma. Repeated bleeding from small, friable vessels 3 within these membranes may for the expansion of some CSDH's.

Prevalence

It has a peak incidence in the sixth and seventh decade of life.[l4] In a study of 64 cases Fogelholm and Waltim[15] estimated an incidence of 1,72/10000 per year, the incidence increasing steeply with advancing ages up to 7, 35 I 100 000 per year in the age group 70 -79 years. In the United States of America the incidence of CSDH peaks in the fifth through to seventh decade of life. The male-to-female ratio is 2:1. The morbidity and mortality rates associated with surgical of CSDH have been estimated at 11 % and 5% respectively.[16]

The incidence of CSDH is estimated at 1.7-18 per 100’000 people, rising up to 58 per 100’000 people in patients above the age of 65 [1-4]. The average age of patients with CSDH is approximately 63 years old [5]. As the population continues to mature, incidence is expected to double by the year 2030 [6, 7]. A large demographic study found the prevalence of CSDH in patients older than 65 to be significantly higher (69% vs. 31%) [8]. In addition, men are more frequently affected than women (64% vs. 33%). In 77% of the cases, the patient has suffered a fall in the past and 41% of the patients were either treated with oral anticoagulants or platelet aggregation inhibitors. The reported recurrence rates range from 2.3% to 33% [8-11]. The most common risk factors are: advanced age, alcohol abuse, seizures, cerebrospinal fluid (CSF) shunts, coagulopathies, blood thinners, and patients at risk for falling (e.g. hemiplegia). In 20-25% of the cases, CSDHs are bilateral [5]. CSDH remains one the most frequent diagnoses in neurosurgical practice.

Pathophysiology

CSDH are more common in

Cerebral atrophy in old age.

Dementia.

Alcoholism.

CSDH associated with-

Impaired coagulation of blood.

Repeated minor head injuries.

In younger persons: the focal cerebral atrophy associated with an arachnoid cyst.

Ventricular and lumber drains & lumber punctures:

Drop the intraventicular pressure.

Open up the subdural space.

Predispose patients to CSDH.

The stretched bridging veins (Between the dura mater & arachnoid mater) easily torn as a result of minor trauma, leading to hemorrhage in the subdural space.

One day after hemorrhage-

Outer surface of the hematoma covered by a thin layer of fibrin & fibroblasts.

Blood in the subdural space triggers inflamation.

On the 4th day after hemorrhage-

Migration & proliferation of the fibroblast leads to –

Formation of neomembrane with fragile neocapillaries.

During the next two weeks-

Further microbleeding.

The outer membrane progressively enlarges.

The fibroblasts invade the haematoma & form a thin membrane.

Liquefaction of the haemtoma occurs due to the presents of phagocytes.

The haemtoma either reabsorb spontaneously or slowly increase in size resulting in CSDH.

Significantly higher levels of-

Proinflamatory mediators (Interleukin-2, 5, 6, 7) &

Anti-inflamatory mediators.

Evoke a local aseptic inflamatory & inflamation induced angiogenic reaction.

Angiogenic reaction leads to formation of neomembranes cause repeated microbleeds into the hematoma cavity.

To discuss all relevant aspects concerning the pathophysiology and treatment of the CSDH, we focus on the following subjects:

Anatomic consideration and membranes

Inflammatory pathways

Angiogenesis and growth factors

Coagulopathy and hyperfibrinolysis and exudation

Proteome and hormones

Nonsurgical treatment of CSDH

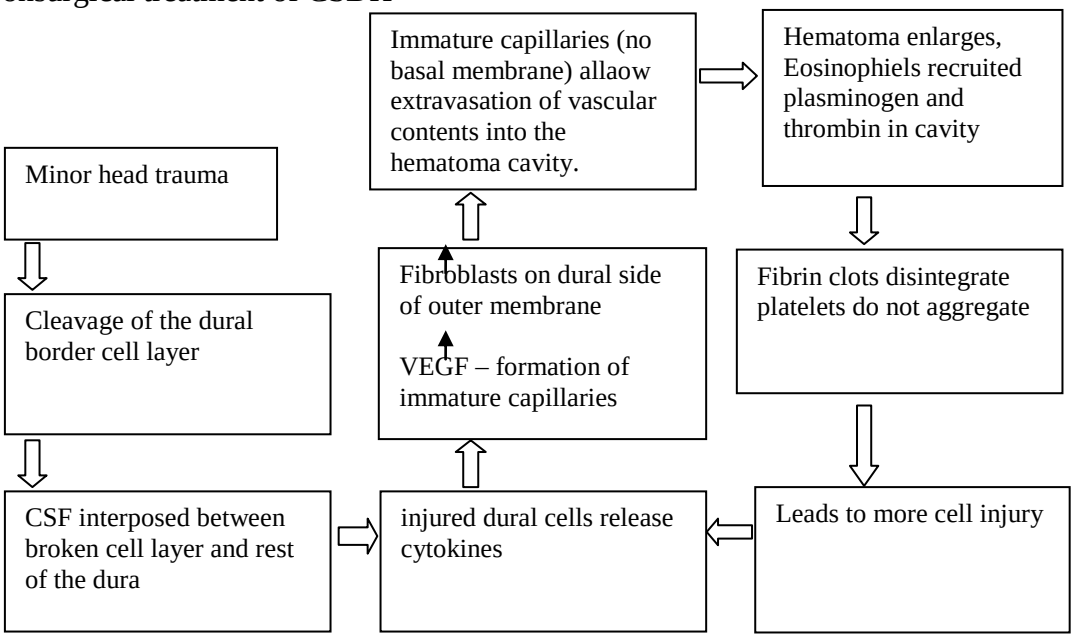


Figure 4: The pathophysiology of chronic subdural haematoma; this cycle perpetuates CSF= cerbrospinal fluid; VEGF=vascular endothelial growth factor.

Anatomic Consideration and Membranes

The Subdural Space

The subdural space was described in several human and anatomic studies and in a review by Haines et al.[36,37] CSDH was initially regarded as a thin lamina of fluid between the dura mater and the arachnoid mater, a well-accepted theory accepted even in the twentieth century.[38] However, the so-called subdural space is a layer of cells called dural border cells, which have junctions that are less tight than the rest of the properly bound dura and arachnoid mater.[37] In 1936, Munro had already shown in his surgical pathology series that within 24 hours after the event responsible for the initiation of CSDH, fibroblasts lining the underside of the dura, in the vicinity of dural border cells, begin to form an outer membrane that is for the most part fully developed within 1 week.[39] Within 3 weeks, the inner membrane, much thinner, is also fully constituted. These findings were later confirmed through electron microscopy.[40]

The trigger for the chain of events leading to a CSDH with mass effect is likely to be a minor traumatic event that causes tearing of the dural border cell layer and the extravasation of cerebrospinal fluid and blood in the now existing subdural space. The mass effect appears because of extravasation of CSF in the subdural space and not as a result of the hematoma itself.[41] The CSF sets a cascade of inflammation, impaired coagulation, fibrinolysis, and angiogenesis. Before discussing these parameters in more detail, we focus on the role of the membranes.

The Membranes

The external membrane has abundant blood vessels, with giant capillaries having a large lumen similar to veins, but without pericyte investment or smooth muscle cells. These capillaries show abnormal permeability through the large gaps and sparse basal membrane permitting the direct spill of vascular contents in the extravascular space.[42] There are also wide gaps, 0.4 mm, between adjacent endothelial cells, facilitating the transport of substances and migration of cells as they would from intercellular gaps of venules in inflamed tissue. During the course of disease, vesicles are seen within capillaries pointing toward the evacuation of hematoma contents.[17] Furthermore,

the membrane contains active fibroblasts, a large number of collagen fibrils, and migrating cells. The inner membrane contains 4 sepa-rate layers, from external to internal: the hematoma surface; the intermediate layer, in which sometimes eosinophils and edematous fluid are found in the dilated extracellular space; the arachnoid surface layer with blood pigments, fibrins, and Fibrinoid substance among loosely tied collagen fibrils and elastin; and the final layer, in which the cells scarcely show the tight intercellular junctions such as des-mosomes that are to be expected from the arachnoid mater.[43]

Inflammatory Pathways

With progression of disease, fewer cellular and vascular structures and more fibrous tissue are present in the membranes. Fibroblasts are recruited by basic fibro-blast growth factor and the release of chemokines. The fibroblasts organize on the dural side of the outer membrane. Some of these fibroblasts become myofi-broblasts, which in electron microscopy studies resemble smooth muscle cells. Their presence might be attributable to a physiologic reaction also seen in athero-matous plaques or granulation tissue.[44] Myofibroblasts produce chemokines to recruit inflammatory cells to the inflammation epicenter.[45] The dural border cells organize the inner membrane with help from the arachnoid mater, which becomes adherent to it.

Inflammation in CSDH is a local pro-cess, as shown by normothermia and absence of increased/augmented systemic inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. Cytokines, such as the proin-flammatory tumor necrosis factor a, interleukin 6 (IL-6), chemokine IL-8, and the antiinflammatory IL-10, are present at higher concentrations in CSDH fluid than in serum.[46] Because CSDH is an encapsulated collection, it is unlikely that CSF may permeate the subdural cavity once CSDH is formed.[46] Therefore, the likely source of cytokines is represented by fibroblasts, endothelial cells, and inflammatory cells found in the membrane, because these types of cells are known to secrete inflammatory markers in response to bleeding.[47]

IL-6 can cause enlargement of endo-thelial gap junctions with subsequent increased vascular permeability,[48] probably via the JAK/STAT3 (Janus kinase-signal transducer and activator of transcription) pathway,[49] a phenomenon that is also described in the membrane of the CSDH. IL-8 promotes leukocyte recruitment to sites of

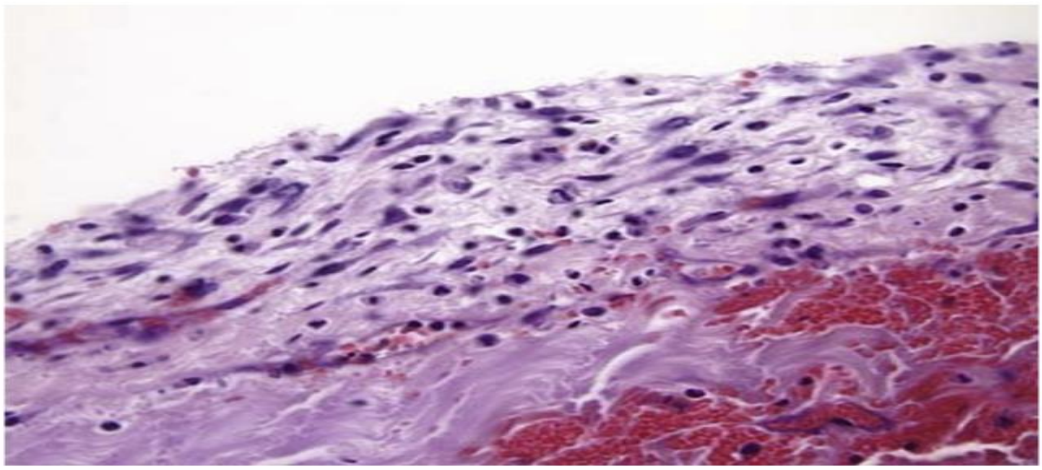


Figure 5. Histologic study of the outer membrane of chronic subdural hematoma. Notice the erythrocytes are inferior and the proliferating fibroblasts are superior. This histologic specimen is dated 7 days after the episode of bleeding.

inflammation or injury by activating integrins and subse-quently by promoting migration through the extracellular matrix.[50,51] It is a potent angiogenic factor, which may partly explain why it is significantly increased in the layering type of hematoma.[46]

On magnetic resonance imaging,T1 hyperintense CSDH showed higher concentrations of IL-6 and IL-8, whereas T2 hyperintense hematomas showed higher concentrations of b-trace protein in the subdural fluid compared with the serum. These findings seem to be associ-ated with recurrences in hyperintense T1 hematomas and CSF admixture in hyper-intense T2 hematomas, respectively.[52]

Levels of IL-10 seem also to be increased in CSDH hematoma fluid, even although it is an antiinflammatory cyto-kine. The patients with increased levels of IL-10 also have higher levels of IL-6 and IL-8,[53] but layering hematomas were correlated with a lower IL-10 level in the fluid.[54] A high level of IL-6 and IL-8 with a high level of IL-10 is indicative of nonspecific inflammation and may sug-gest that the process can be self-limiting.[53] The membranes show prominent infil-tration of degranulated eosinophils and lymphocytes, whereas within the hema-toma, eosinophil counts are only slightly increased.[55] Lymphocytes release chemoattractants, drawing the eosinophils to the site of injury.[56] Most likely, eosinophils promote hyperfibrinolysis by the release of plasminogen, fibrosis in the fibroblasts of the outer membrane, and phagocytosis of metabolites, and even resorption of hematoma products.[57-59]

Another inflammatory pathway is the cyclooxygenase 2 (COX-2)eprostaglandin E_2 (PGE_2) pathway.[60] COX-2 triggers the synthesis of PGE_2, which in turn stimulates the overexpression of vascular endothelial growth factor (VEGF), responsible for induction of angiogenesis. COX-2 is over-expressed in the outer membrane, especially in endothelial cells and in inflammatory cells. Among these cells are numerous CD-68-positive macrophages, which may cause the increased level of PGE_2 in the subdural fluid compared with serum.

Angiogenesis and Growth Factors

VEGF is one of the key angiogenic factors, originally described as a tumor-secreted protein named the vascular permeability factor, which causes substantial vascular leakage.[61] VEGF and the proangiogenic factor angiopoietin 2, create an unstable condition with the continuous formation of new and immature capillaries causing extravasation and recurrent microbleeds.[62]

Also, hypoxia-inducible factor 1a plays an important role in the process of vessel formation. It is induced by hypoxia and strongly present in the outer membrane and correlates strongly with VEGF pres-ence.[63] Levels of VEGF and basic fibroblast growth factor are higher in subdural fluid than in serum and show a strong presence in the neomembrane as well.[61,64]

VEGF is produced by macrophages, plasma cells in the membranes, and endothelial cells of the fragile micro-capillaries of the outer membrane. It is suggested that one of the therapeutic as-pects of surgical drainage of the hema-toma and washing of the subdural space disrupts the cycle of autocrine cell stimu-lation of VEGF by strongly decreasing its level in the hematoma cavity.[65]Besides VEGF, which regulates endothelial cell survival through the phospha- tidylinositol 3-kinase/Akt/endothelial nitric oxide synthase pathway,[66] 2 other pathways contribute to the CSDH pathogenesis. The Ras/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, activated by IL-6 and VEGF, has a role in endothelial cell proliferation and migration and the transforming growth factor b/activin receptorlike kinase 1 pathway, which is essential for the formation and remodel-ing of new vessels. These pathways all represent intracellular ways in which VEGF exerts its effects. Further research into the upregulation and downregulation of these pathways, as well as into the factors that

influence them, is required to draw the line between normal endogenous repair processes and pathologic VEGF activation and possible halting of its effects.

The exudation rate of VEGF and albu-min in the subdural fluid can be related to computed tomography appearance, using the Nomura classification.[67] Nomura made a subdivision into 5 types of CSDH according to their appearance on CT: high density, isodensity, low density, mixed density, and layering. The mean VEGF concentration was highest in mixed density hematomas.[68,69] There is also a significant correlation between the VEGF concentration and MRI appearance.[70-72]

Coagulopathy, Hyperfibrinolysis, and Exudation

Next to inflammation and angiogenesis, coagulopathy, hyperfibrinolysis, and protein exudation play important roles in the maintenance of the hematoma and explain why there is continuous bleeding in the cavity and no clot.

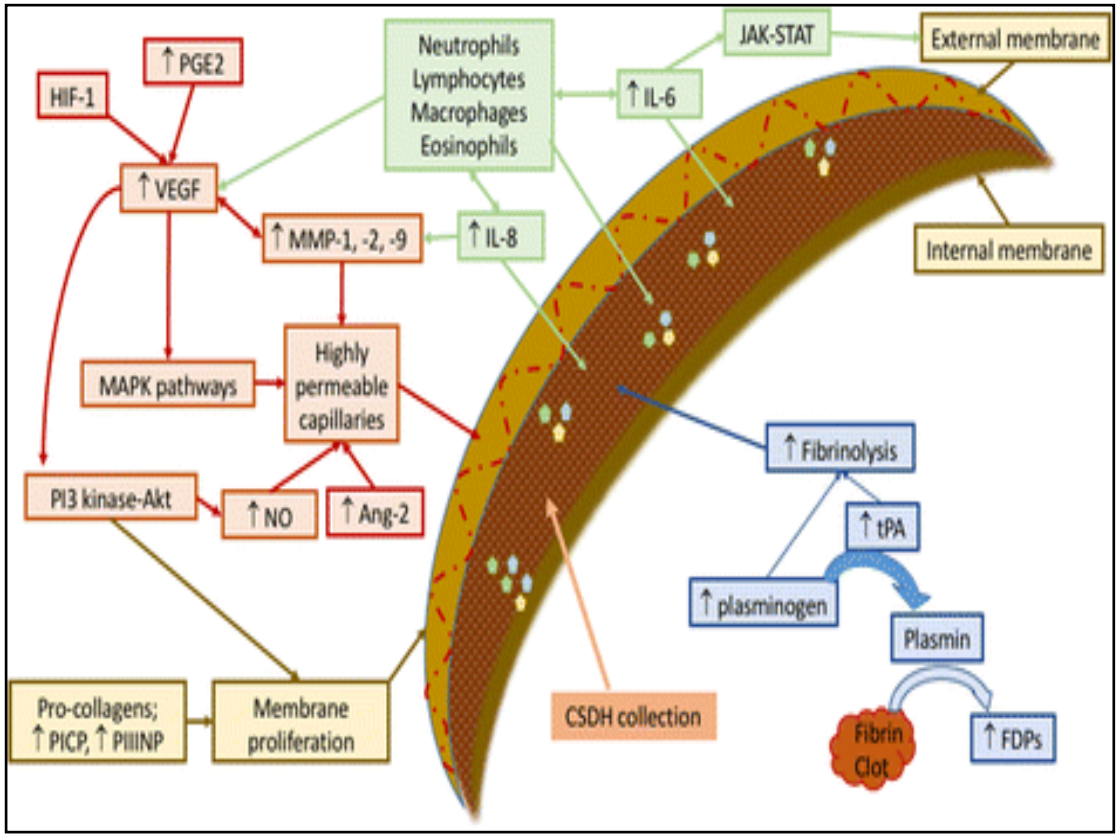


Fig 6: Pathophysiology of CSDH

Table 1: Factors Involved in the Pathophysiology of Chronic Subdural Hematoma

Inflammatory pathway	
Fibroblasts	(Myo)fibroblasts produce chemokines
bFGF (basic fibroblast growth factor)	Recruits fibroblasts
Lymphocytes	Release chemoattractants drawing the eosinophils to the site of injury
Eosinophils	Releases plasminogen, promotes fibrosis in the fibroblasts, phagocytosis of metabolites, and resorption of hematoma products
IL-8 (interleukin)	Inflammatory marker; promotes leukocyte recruitment to sites of inflammation or injury
IL-6 (interleukin)	Inflammatory marker; enlarges the endothelial gap junctions, which increases the vascular permeability
IL-10 (interleukin)	Antiinflammatory marker, lower IL-10 in layering hematomas. If IL-6, IL-8, and IL-10 are high, this is indicative of a nonspecific inflammation and suggests a self-limiting process
Janus kinase-signal transducer and activator of transcription pathway	Effector pathway by which IL-6 exerts its pathogenic effects in CSDH
Angiogenesis and Growth Factors	
HIF-1a (hypoxia-inducible factor 1a)	Proangiogenic factor, increased in the subdural fluid and neomembrane
MMP-9 (matrix metalloproteinase 9)	Reduced absorption of CSDH because of increased vascular permeability, enhanced inflammation, and reduction of vascular maturation
MAPK pathways (mitogen-activated protein kinase)	Regulates proliferation and migration of endothelial cells, possibly activated by VEGF and IL-6
PI3/Akt/endothelial nitric oxide synthase pathway	VEGF regulates endothelial cell survival through this pathway
Transforming growth factor b/activin receptorlike kinase 1(ALK-1) pathway	Essential for the formation and remodeling of new vessels
Coagulopathy, Hyperfibrinolysis, and Exudation	
Plasminogen	The inactive precursor of plasmin
t-PA (tissue plasminogen activator)	Activates plasminogen, which is converted to plasmin. Activated plasmin degrades coagulation factors V, VIII, and XI
Thrombin	Thrombin catalyzes the conversion of fibrinogen into fibrin
FDPs (fibrinogen degradation products)	Includes fibrin monomer and D-dimers. D-dimers inhibit platelet aggregation and fibrin polymerization
TM (thrombomoduline)	Thrombin receptor on endothelial cells of the

	capillaries that inhibits blood clotting by binding with thrombin and the activated protein C. It is expressed and increases after vascular endothelial injury
Ang-2 (angiopoietin 2)	Proangiogenic factor that, in combination with VEGF, leads to the formation of immature capillaries
TGFbI (transforming growth factor-b-induced protein Ig-H3)	Protein, responds to tissue injury and has a role in wound healing. In CSDH, it plays an important role in the proliferation of the membrane and the meningeal reaction to the subdural collection
PICP (propeptide of type I collagen) and PIIINP (aminoterminal propeptide of type III procollagen)	Increased in the subdural fluid; indicating a long-lasting upregulation of collagen synthesis
CSDH, chronic subdural hematoma; VEGF, vascular endothelial growth factor.	

The inflammatory mediators stimulate the vascular permeability and release tis-sue plasminogen activator (t-PA) from endothelial cells. The level of t-PA in the hematoma fluid was found to be signifi-cantly higher than in plasma.[73] These levels correlated with the size of the hematoma and clinical status of the patient: patients with stupor and coma had significantly higher levels of t-PA than did patients with headache or somnolence. The t-PA levels also related to the aspect on the CT scan, on which layering hematomas show higher levels.[73] t-PA activates plasminogen, which is then converted to plasmin. The activity of plasmin in the subdural fluid together with normal plasmatic levels shows local hyperfibrinolytic activity.[74] Moreover, hematoma fluid contains a low amount of plasminogen when compared with serum, because of its ongoing conversion to plasmin, and a higher amount of fibrinogen degradation products, including fibrin monomer and D-dimers. D-dimers inhibit platelet aggregation and fibrin polymerization, whereas the activated plasmin degrades coagulation factors V, VIII, and XI.[75] Thus, the consequences are an impaired platelet function, a defective fibrin clot, and an important hemostatic imbalance.[76] Subdural fluid collected 24 hours after surgery showed reduced t-PA and fibrinogen degradation products levels,[77] signifying the re-establishment of a bal-ance between coagulation and fibrinolysis.

Thrombin also plays an important role in the progression of CSDH. The thrombin-antithrombin III complex and prothrombin fragments 1 and 2 are nonsignificantly increased in subdural hygroma and significantly increased in CSDH, whereas levels of D-dimers, indi-cating fibrinolytic activity, are only increased in CSDH. Thrombomodulin is expressed and increased after vascular endothelial injury. It is a thrombin recep-tor on endothelial cells of the capillaries that inhibits blood clotting by binding with thrombin and the activated protein C.[54] It showed higher levels in mixed density hematomas and the highest level in laminar types.[78] The extrinsic clotting system becomes defective in the development of CSDH, and the switch from subdural hygroma to CSDH occurs when fibrinolysis begins to manifest.

Proteome and Hormones

The Subdural Hematoma Proteome

A recent study has characterized the subdural he-matoma proteome,[79] in which 1100 proteins were analyzed for differences with serum levels. In total, levels of 11 proteins were increased, most being regulators of coagulation and fibrinolysis. Among those proteins were fibrinogen, corresponding to the state of hyperfibrinolysis and hemoglobin a and b levels, suggesting ongoing erythrocyte lysis. Another protein with increased level is transforming growth factor be induced (TGFbI) ig-h3,[79] which is associated with tissue injury and wound healing, making it probably responsible for the proliferation of the membrane and the meningeal reaction to the subdural collection. Complement values were shifted (C3ca) and decreased (C4c), suggesting a role for complement in the inflammatory reaction that characterizes CSDH, but its specific role has yet to be explored.

Two reports stated that propeptide of type I collagen and the aminoterminal propeptide of type III procollagen were 78-fold to 156-fold higher than in serum from the period of 10e85 days after injury, indicating a long-lasting upregulation of collagen synthesis.[80] Moreover, this increase is time dependent in the first 2 weeks and remains high for more than 3 months, whereas in dermal wound healing, these levels normally decline 3 weeks after injury.[81,82] The dural fibrosis reaction stays active even longer than the one observed in subarachnoid hemorrhage, which subsides after a month.

Hormones

An intriguing area of research was proposed in 1977 by observing high urinary estrogen levels in male patients with CSDH, suggesting that this might play a role in the pathogenesis of the disease.[83] In 1984 and later in 1992, positive staining for estrogen and progesterone receptors in the membrane of hematomas was shown. Estrogens might influence the vascularized membranes directly, including stimulating synthesis of t-PA. This characteristic could be more pronounced in men whose vascular system is less adapted to high values of estrogen.[84,85] However, these theories could not be reproduced in a later study.[86]

Nonsurgical Treatment of CSDH

Dexamethasone. Steroids might be an op-tion in the nonsurgical treatment of CSDH. Dexamethasone is known to be antiinflammatory and has antiangiogenic effects. Moreover, it is able to inhibit the formation of new blood vessels. Over the past decades, dexamethasone has been assessed in multiple studies as mono-therapy or as an adjunct to BHC.[87-93] Dexamethasone is a noninvasive treat-ment and might significantly reduce mortality and lead to a better outcome.[94] Also, in some patients, this treatment led to shorter hospitalization, making it more cost-effective compared with BHC.

The downside of dexamethasone use is a higher complication rate such as dia-betes, infections, and mental changes. The mortality in studies using dexamethasone for treatment of CSDH varies between 0.8% and 4%.[94], Thotakura and Marabathina identified several variables (female sex, limited midline shift and hematoma thickness, and lower CT attenuation values) that are associated with a good outcome after conservative treatment with dexametha-sone.[92] Zhang et al.[95] conclude that in patients with recurrent CSDH, dexamethasone treatment might avoid reoperation. Prospective studies on the role of dexamethasone in the treatment of CSDH are ongoing.[96,97]

The entity of CSDH was first described by Virchow in 1857 [12]. He named it “pachymeningitis haemorrhagica interna”, recognizing its inflammatory and hemorrhagic elements [12]. Interestingly, the subdural space is a virtual space which

does not exist in healthy individuals, as the dura and arachnoid are tethered by a layer of dural border cells (DBC)[1, 7, 13, 14]. The DBC is characterized by a paucity of tight junctions and an enlarged extracellular space containing amorphous material [7, 14].

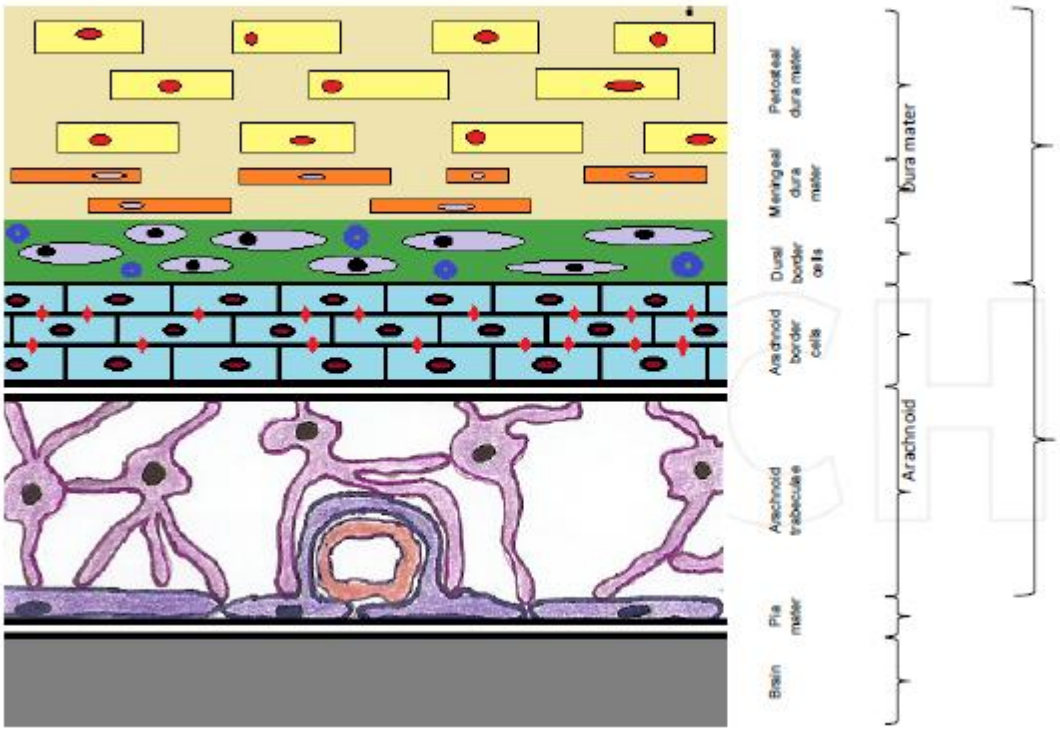


Figure 7: Schematic representation of the ultrastructure of the meninges (adapted from Haines and Santarius et al [7,14]. The dura mater is composed of fibroblasts and large amounts of collagen. The arachnoid barrier cells are supported by a basement membrane and bound together by numerous tight junctions (red diamonds). The dural border cell layer (green) is formed by flattened fibroblasts with no tight junctions and no intercellular collagen.

It is therefore a relatively loose layer positioned between the firm dura matter and arachnoid. The subdural space is a potential space that can form within the dural border cell layer. The bridging veins passing through the dural border cell layer are a potential source of bleeding. With increasing brain atrophy, the arachnoid is pulled away from the dural layer, which remains attached to the skull. The resultant force stretches the DBC layer and the veins traversing it (bridging veins). Any minor additional force can cause these veins to tear, causing a leakage of blood into the DBC and creating an acute SDH. Therefore, the majority of cSDHs are caused by an undiagnosed trivial head injury, primarily in patients with brain atrophy. This trauma leads to a minor acute SDH. Today, it is widely accepted that cSDHs are a result of

the failure of small acute SDH to heal. Following the initial trauma and development of a cSDH, fibrin deposition occurs, followed by organization, enzymatic fibrinolysis and liquefaction of the hematoma. The blood in the subdural space triggers an inflammatory response. After approximately two weeks, an inner (cortical) and outer (dural) neomembrane is formed inside the DBC layer through dural collagen synthesis and fibroblast spread [1, 15, 16]. In growth of fragile neocapillaries into the neomembranes of the hematoma can lead to further microbleeds within the subdural space [1]. Less commonly, the SDH may result from arterial ruptures (20-30%), hemorrhage into an existing subdural hygroma or spontaneously, mostly influenced by anticoagulants or antiplatelet therapy [1, 17, 18].

The factors responsible for the maintenance or enlargement of cSDH over time are still ambiguous. It is most likely influenced by multiple factors, which vary from case to case. Over the years, several theories have been debated:

a. "Osmotic theory": The initial acute hematoma resorbs through fibrinolysis and the remaining resorption products within the subdural space lead to an elevated osmotic gradient. Due to the osmotic pressure, CSF follows the osmotic gradient and drifts into the subdural space, leading to an expansion of the hematoma [19, 20].

b. "Oncotic theory": Due to the low oncotic pressure inside the hematoma capsule, blood permeates from the dural vessels into the subdural space, leading to an expansion of the hematoma [16].

c. "Microbleeds theory": As they lack a muscle layer and periocytes, the neocapillaries forming inside the neomembrane are fragile. This leads to repeated microhemorrhaging into the subdural space and expansion of the hematoma [1, 7, 21].

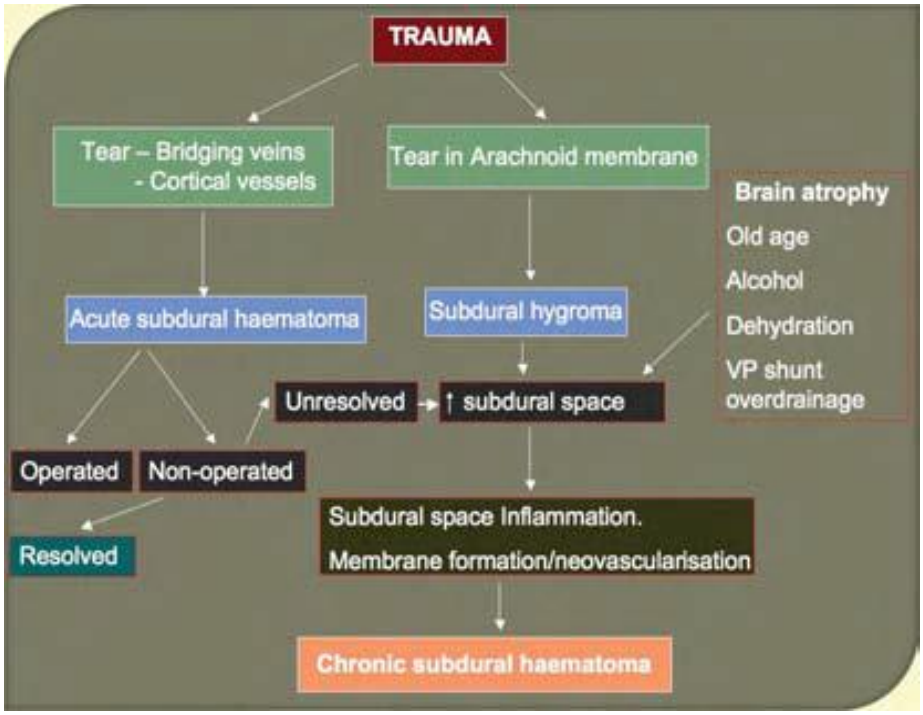


Figure 8: Flow chart of chronic subdural haematoma

Risk factors

As previously mentioned dementia and alcoholism causes' cerebral atrophy, which increase in the space between the brain and the skull, stretching the bridging veins and making them more vulnerable to trauma. Advancing age especially in the fifth and sixth decade of life will also contribute to this phenomenon. Other risk factors include a head injury, anticoagulants or antiplatelet drugs (aspirin), bleeding tendencies, epilepsy and patients with chronic renal failure. It is reported by Adhiyaman et al.[14] that as many as 24% of patients with CSDH are on warfarin. Conditions such as shunts,[18] which may cause low intracranial pressure, hypertension and arteriosclerosis, may also indirectly contribute the illness.

Clinical manifestations, signs and symptoms

Altered mental state

The presentation in the elderly (50% - 70%) altered mental state.[14] manifest varying degrees of confusion, drowsiness or coma. Acute delirium may be very difficult to differentiate from behavioural or psychotic symptoms. Some patients are even considered to be suffering from major psychiatric illness because of depressive and paranoid symptoms. Also the diagnosis may be very easy to overlook in patients with psychiatric neurological illnesses in whom any change in behaviour or functional usually attributed to their pre-existing illness.

Focal neurological deficit

Weakness of the limbs usually mild but drowsiness is of proportion to the degree of neurological deficit. Mostly the deficit is contralateral but there are reports of ipsilateral symptoms. Focal signs be extremely subtle and variable.

Headache

The incidents of headaches vary and have the following characteristics. The headache typically of sudden onset, severe, associated with vomiting, and exacerbated by coughing, straining or exercise.

Falls

Recurrent falls is a significant risk factor of CSDH. In a study of 354 cases by Baechli, 77% of patients had history of a fall.[19]

Seizures

Epilepsy is traditionally thought to be a rare presentation, however patients with epilepsy are more likely to have recurrent head injuries and develop cerebral atrophy much earlier in life.

Others

Luxon and Harrisons reported these signs (in decreasing order of frequency): Papilloedema, reflex asymmetry, extensor plantar response, dysphagia, neck stiffness, hemianopia and dysarthria. Meagher and Young[20] are of the opinion that a gait abnormality is another common sign of CSDH. The following clinical signs are atypical (uncommon) presentations of CSDH:

Isolated neurological deficits

Patients presenting with vertigo and nystagmus, upward gaze palsy and isolated oculomotor palsy due to CSDH have been reported. Increase intracranial pressure causing uncal herniation and stretching of cranial thought be the mechanism involved.

Extrapyramidial syndromes

Parkinsonism is a well-recognized phenomenon

Rare neurological syndromes

Gerstmann's syndrome (right-left disorientation, finger agnosia, agraphia and acalculia) and progressive quadriparesis due to SDH has been reported in the literature. These patients made a good recovery after the evacuation of the haematoma. Fogelholm et al.[15] have observed that while headaches and papilloedema were more frequently found in younger patients, older patients had a higher frequency of mental symptoms and hemiparesis. Similarly, in the study by Liliang and Tsaill[18] it was found that headaches and vomiting were more prevalent in the younger age group and mental symptoms in the older group.

So the following clinical signs commonly present with CSDH

Altered mental state

- Confusion
- Drowsiness
- Coma

Focal neurological deficit:

Weakness of the limbs

Headache with vomiting

Recurrent falls

Seizures

Papilloedema

Extensor plantar response

Dysphagia

Neck Stiffness

Hemianopia

Dysarthria

Gait abnormality

Vertigo

Nystagnus

Oculomtor Palsy

ICP

Gerstmann's Syndrome

Right-left disorientation

Finger agnosia

Agraphia &

Acalculia

Presentation

Patients can present with one or more of the following clinical scenarios:

Headache

Nausea

Vomiting

Impaired level of consciousness

Papilloedema

Hemiplegia

Dysphagia

Seizures

Focal

Generalized

Investigations

Computed tomography remains the preferred imaging modality and CSDH is classically described as a hypodense sickle-shaped extra axial fluid collection with evidence of surrounding mass effect. Where the haematoma evolves as a result of an acute bleed its density and appearance change with time in relation to the surrounding cortical surface.

Three phases are described:

Hyperdense (0-7 days)

Isodense (1-3 weeks)

Hypodense (>3 weeks)

Diagnosis

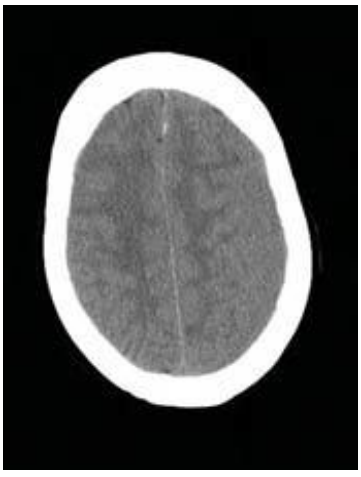


Figure 9: CT scan of a 62-year-old lady with leukemia and low platelets showing an isodense left sided chronic subdural haematoma. She presented with a history of headache. The density of the haematoma is the same as the adjacent cortical surface and can be easily missed.

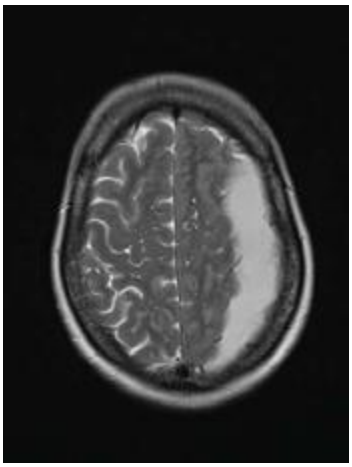
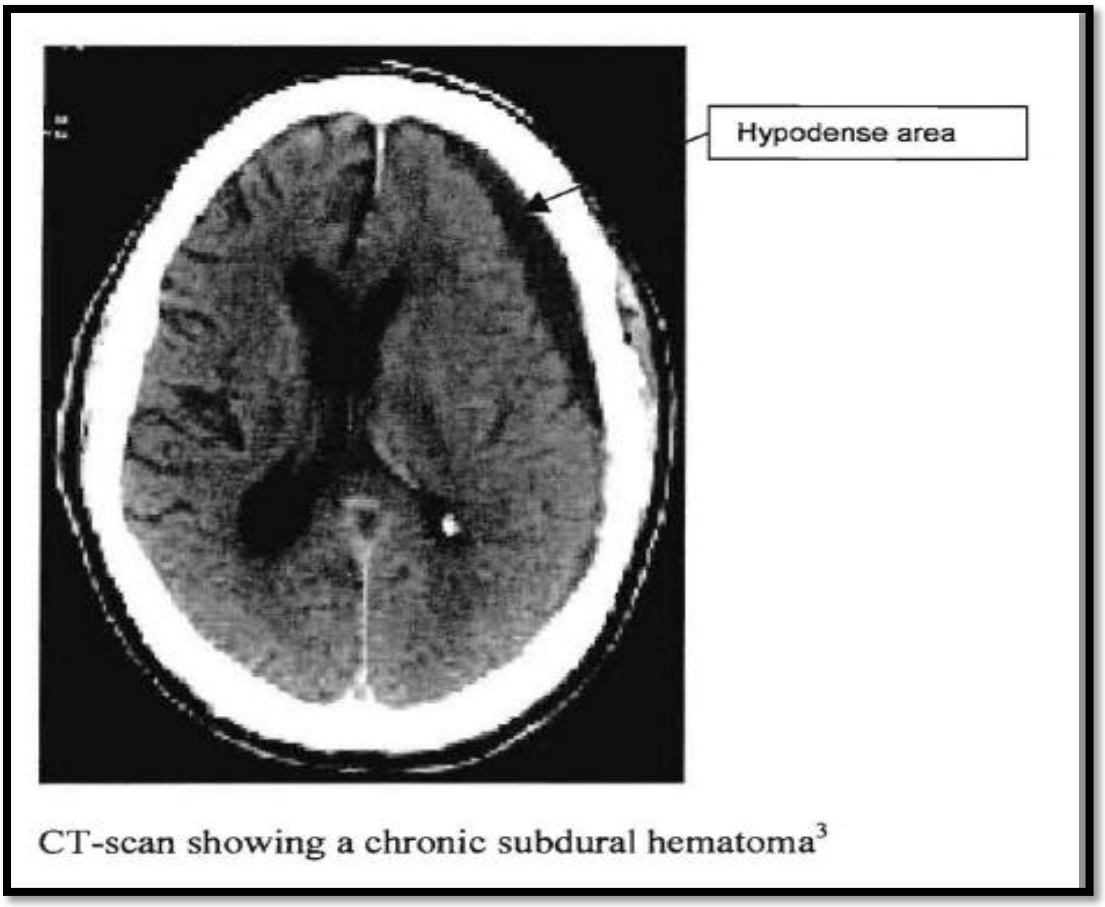


Figure 10: The same patient underwent an MRI scan which as shown on the T2 weighted sequence confirms a left sided chronic subdural haematoma.

In the majority of cases a CSDH is visualised as a mass comprising hypo and hyperdense signal characteristics. Bilateral isodense SDH's may result in a misdiagnosis due to difficulties in identifying cerebral cortex and the absence of midline shift (Figure 2). A contrast CT scan will show any enhancing membranes and can delineate the haematoma more precisely. MRI is also a useful adjunct in some cases. For the most part, T1 and T2 images both show the haematoma to be hyperintense relative to brain and CSF.6 The change of signal intensity correlates with the length of time the haematoma has been present and the breakdown of blood in the haematoma capsule.

CT-scan is the gold standard to make the diagnosis of CSDH. Prior CT-scans, cerebral angiography was used. MRI can also be used especially to diagnose subacute and bilateral subdural haematomas. The blood appears as crescent-shaped hyperdense lesions in acute SDH. Subacute SDH are isodense and more difficult to identify. CSDH appears hypodense, the iron in the blood is phagocytised.[13]



CT-scan showing a chronic subdural hematoma[3]

Figure 11: CT scan findings

Classification of Corticosteroids

Corticosteroid	Equivalent dose (mg)	Glucocorticoid potency	Mineralocorticoid potency	Plasma half-life (minutes)	Biological half-life (hours)
Short Acting					
Cortisone	25	0.8	2+	30-90	8-12
Hydrocortisone	20	1	2+	60-120	8-12
Deflazacort	6			90-120	<12
Intermediate Acting					
Prednisone	5	4	1+	60	24-36
Prednisolone	5	4	1+	115-212	24-36
Methylprednisolone	4	5	0	180	24-36
Triamcinolone	4	5	0	78-188	24-36
Long Acting					
Dexamethasone	0.75	20-30	0	100-300	36-54
Betamethasone	0.6-0.75	20-30	0	100-300	36-54

How steroids control inflammation

Corticosteroids (also known as glucocorticosteroids, gluco-corticoids or just steroids) are among the most widely used drugs in the world and are effective in many inflammatory and immune diseases. The most common use of corticosteroids is in the treatment of asthma, where inhaled corticosteroids have become first-line therapy and by far the most effective anti-inflammatory treatment. There have been important advances in understanding the molecular mechanisms whereby cortico-steroids suppress inflammation so effectively in asthma and other inflammatory disease, based on recent developments in understanding the fundamental mechanisms of gene transcrip-tion and cell signalling in inflammation (Barnes & Adcock, 2003; Rhen & Cidlowski, 2005). This new understanding of these new molecular mechanisms also helps to explain how corticosteroids are able to switch off multiple inflammatory pathways, yet remain a safe treatment. It also provides insights into why corticosteroids fail to work in patients with inflammatory diseases such as chronic obstructive pulmonary disease and cystic fibrosis (Barnes et al., 2004).

The Nobel Prize for Medicine and Physiology in 1950 was awarded to Kendall and Reichstein, who had independently*Author for correspondence; E-mail: p.j.barnes@imperial.ac.uk isolated and synthesised cortisol and then adrenocorticotropic hormone and Philip Hench, a rheumatologist work-ing at the Mayo Clinic, who had described the dramatic efficacy of ACTH in patients with rheumatoid arthritis. Only 6 months after Hench's discovery, Boardley and colleagues at John Hopkins University showed that ACTH had dramatic benefits in patients with asthma (Boardley et al., 1949). Oral corticosteroids were subsequently shown to be as effective but their use was limited by systemic side effects that are well known today. The breakthrough that revolutionised asthma therapy was the introduction of inhaled corticosteroids that had topical activity in 1972 (Brown et al., 1972).

The predominant effect of corticosteroids is to switch off multiple inflammatory genes (encoding cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors and proteins) that have been activated during the chronic inflam-matory process. In higher concentrations they have additional effects on the synthesis of anti-inflammatory proteins and postgenomic effects. This review discusses how corticosteroids so effectively switch off multiple inflammatory genes in steroid-

sensitive inflammatory diseases, such as asthma, whereas fail to control inflammation in other inflammatory diseases, such as COPD.

Molecular mechanisms of chronic inflammation

Chronic inflammatory diseases, such as asthma, COPDrheumatoid arthritis and inflammatory bowel disease, involve the infiltration and activation of many inflammatory and immune cells, which release multiple inflammatory medi-ators that interact and activate structural cells at the site of inflammation. The pattern of inflammation clearly differs between these diseases, with the involvement of many different cells and mediators (Barnes et al., 1998; Barnes, 2004b), but all are characterised by increased expression of multiple inflammatory proteins, some of which are common to all inflammatory diseases, whereas others are more specific to a particular disease. The increased expression of most of these inflammatory proteins is regulated at the level of gene transcription through the activation of proinflammatory transcription factors, such as nuclear factor-kB (NF-kB) and activator protein-1 (AP-1). These proinflammatory transcription factors are activated in all inflammatory diseases and play a critical role in amplifying and perpetuating the inflammatory process. Thus, NF-kB is activated in the airways of asthmatic patients and COPD patients (Hart et al., 1998; Di Stefanoet al., 2002) and is activated in the joints of patients with rheumatoid arthritis (Muller-Ladner et al., 2002) and the vessels of patients with atherosclerosis (Monaco & Paleolog, 2004). The molecular pathways involved in regulating inflammatory gene expression are now being delineated and it is now clear that chromatin remodelling plays a critical role in the transcriptional control of genes. Stimuli that switch on inflammatory genes do so by changing the chromatin structure of the gene, whereas corticosteroids reverse this process.

Chromatin remodelling and gene expression

Chromatin is composed of DNA and histones, which are basic proteins that provide the structural backbone of the chromo- some. It has long been recognised that histones play a critical role in regulating the expression of genes and determines which genes are transcriptionally active and which ones are sup- pressed (silenced). The chromatin structure is highly organised as almost 2 m of DNA have to be packed nucleus. Chromatin is made up of nucleosomes which are particles consisting of 146 base pairs of DNA wound almost twice around an octomer of two molecules each of the core

histone proteins H2A, H2B, H3 and H4. In the last decade it has been shown that expression and repression of genes is associated with remodelling of this chromatin structure by enzymatic modification of the core histone proteins, particu- larly through acetylation of lysine residues. Each core histone has a long N-terminal tail that is rich in lysine residues, which may become acetylated, thus changing the electrical charge of the core histone. In the resting cell DNA is wound tightly around core histones, excluding the binding of the enzyme RNA polymerase II, which activates gene transcription and the formation of messenger RNA. This conformation of the chromatin structure is described as closed and is associated with suppression of gene expression. Gene transcription only occurs when the chromatin structure is opened up, with unwinding of DNA so that RNA polymerase II and basal transcription complexes can now bind to DNA to initiate transcription.

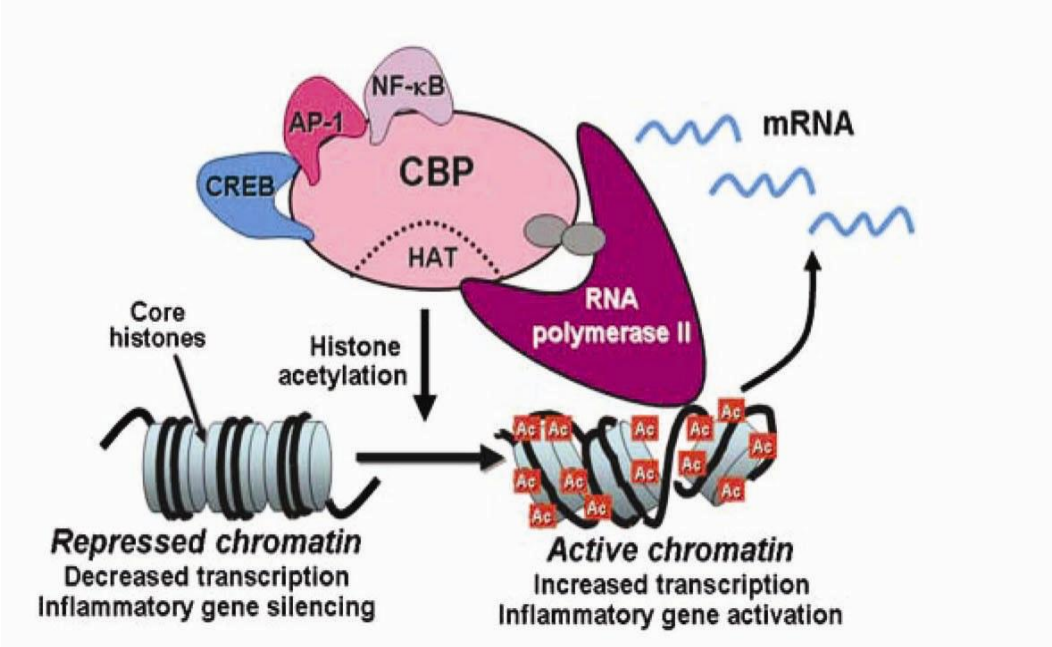


Figure 12: Gene regulation by histone acetylation. Coactivator molecules such as CBP interact with transcription factors such as CREB, AP-1 and NF-kB, resulting in activation of their intrinsic HAT activity. This results in acetylation (Ac) of core histones, opening up the chromatin structure to allow binding on RNA polymerase II, which initiates gene transcription.

Histone acetyltransferases and coactivators

Switching on of inflammatory genes requires the engagement of coactivator molecules which interact with proinflammatory transcription factors, such as NF-kB, that are bound to specific recognition sequences in the promoter region of inflammatory genes. These large coactivator molecules, such as cyclic AMP response element binding binding protein, p300 and p300-CBP associated factor (pCAF), thus act as the molecular switches that control gene transcrip- tion and all have intrinsic histone acetyltransferase activity. This results in acetylation of core histones, thereby reducing their charge which allows the chromatin structure to transform from the resting closed conformation to an activated open form (Roth et al., 2001) (Figure 1). This results in unwinding of DNA, binding of TATA box binding protein, TBP-associated factors and RNA polymerase II, which then initiates gene transcription. This molecular mechanism is common to all genes, including those involved in differen- tiation, proliferation and activation of cells. This process is reversible and deacetylation of acetylated histones is associated with gene silencing. This is mediated by histone deacetylases which act as corepressors, together with other corepressor proteins which are subsequently recruited. These fundamental gene regulatory mechanisms have now been applied to understand the regulation of inflammatory genes in diseases, such as asthma and COPD (Barnes, 2004a). In a human epithelial cell line activation of NF-kB, by expo- sing the cell to inflammatory signals such as IL-1b, tumour necrosis factor-a (TNF-a) or endotoxin, results in acetylation of specific lysine residues on histone H4 (the other histones do not appear to be so markedly or rapidly acetylated) and this is correlated with increased expression of genes encoding inflammatory proteins, such as granulocyte–macrophage colony stimulating factor (Ito et al., 2000).

HDACs and corepressors

The acetylation of histone that is associated with increased expression of inflammatory genes is counteracted by the acti- vity of HDACs, of which 11 that deacetylate histones are now identified in mammalian cells (de Ruijter et al., 2003; Thiagalingam et al., 2003). There is now evidence that the different HDACs target different patterns of acetylation and therefore regulate different types of gene

(Peterson, 2002). HDACs act as corepressors in consort with other corepressor proteins, such as nuclear receptor corepressor (NCoR) and silencing mediator of retinoid and thyroid hormone receptors, forming a corepressor complex that silences gene expression (Privalsky, 2004). In biopsies from patients with asthma there is an increase in HAT and a reduction in HDAC activity, thereby favouring increased inflammatory gene expression (Ito et al., 2002a). Understanding the molecular basis for inflammatory gene expression provides the back- ground for understanding how corticosteroids are so effective in suppressing complex inflammatory diseases that involve the increased expression of multiple inflammatory proteins.

Glucocorticoid receptors

Corticosteroids diffuse readily across cell membranes and bind to glucocorticoid receptors in the cytoplasm. Cyto- plasmic GR are normally bound to proteins, known as mole- cular chaperones, such as heat shock protein-90 (hsp90) and FK-binding protein, that protect the receptor and prevent its nuclear localisation by covering the sites on the receptor that are needed for transport across the nuclear membrane into the nucleus (Wu et al., 2004). There is a single gene encoding human GR but several variants are now recognised, as a result of transcript alternative splicing, and alternative translation initiation (Rhen & Cidlowski, 2005). GRa binds cortico- steroids, whereas GRb is an alternatively spliced form that binds to DNA but cannot be activated by corticosteroids. GRb has a very low level of expression compared to GRa (Pujols et al., 2002). The GRb isoform has been implicated in steroid resistance in asthma (Leung et al., 1997), although whether GRb can have any functional significance has been questioned in view of the very low levels of expression compared to GRa (Hecht et al., 1997). GR may also be modified by phosphorylation and other modifications, which may alter the response to corticosteroids by affecting ligand binding, translocation to the nucleus, trans- activating efficacy, protein–protein interactions or recruitment of cofactors (Bodwell et al., 1998; Ismaili & Garabedian, 2004). For example, there are a number of serine/threonines in the N-terminal domain where GR may be phosphorylated by various kinases. Once corticosteroids have bound to GR, changes in the receptor structure result in dissociation of molecular chaper- one proteins, thereby exposing nuclear localisation signals on GR. This results in rapid transport of the activated GR–corticosteroid complex into the nucleus,

where it binds to DNA at specific sequences in the promoter region of cortico-steroid-responsive genes known as glucocorticoid response elements. Two GR molecules bind together as a homodimer and bind to GRE, leading to changes in gene transcription. Interaction of GR with GRE classically leads to an increase in gene transcription (trans-activation), but negative GRE sites have also been described where binding of GR leads to gene suppression (cis-repression) (Dostert & Heinzel, 2004) (Figure 2). There are few well-documented examples of negative GREs, but some are relevant to cortico-

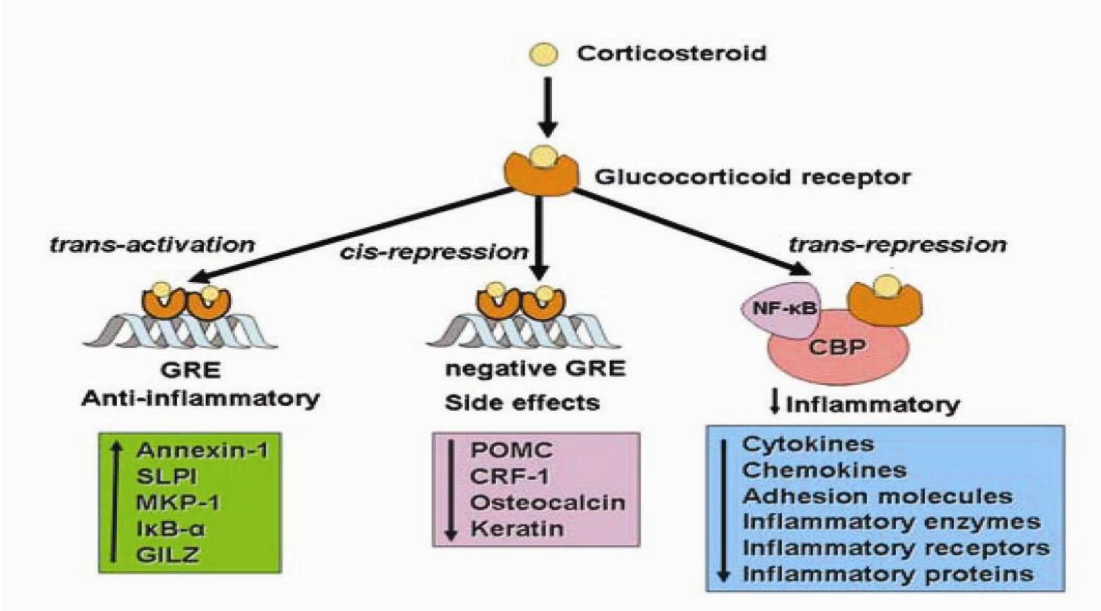


Figure 13: Corticosteroids may regulate gene expression in several ways.

Corticosteroid-induced gene transcription

Corticosteroids produce their effect on responsive cells by activating GR to directly or indirectly regulate the transcription of target genes. The number of genes per cell directly regulated by corticosteroids is estimated to be between 10 and 100, but many genes are indirectly regulated through an interaction with other transcription factors and coactivators. GR homodimers bind to GRE sites in the promoter region of corticosteroid-responsive genes. Interaction of the activated GR dimer with GRE usually increases transcription. GR may increase transcription by interacting with coactivator mole- cules, such as CBP and pCAF, thus inducing histone acetylation and gene transcription. For example, relatively high concentrations of corticosteroids

increase the secretion of the antiprotease secretory leukoprotease inhibitor (SLPI) from epithelial cells (Ito et al., 2000).

The activation of genes by corticosteroids is associated with a selective acetylation of lysine residues 5 and 16 on histone H4, resulting in increased gene transcription (Ito et al., 2000; Ito et al., 2001a). Activated GR may bind to coactivator molecules, such as CBP or pCAF, as well as steroid receptor coactivator-1 (SRC-1) and GR interacting protein-1 (GRIP-1), all of which possess HAT activity (Yao et al., 1996; Kurihara et al., 2002). GR preferentially associate with GRIP-1, which subsequently recruits pCAF (Li et al., 2003).

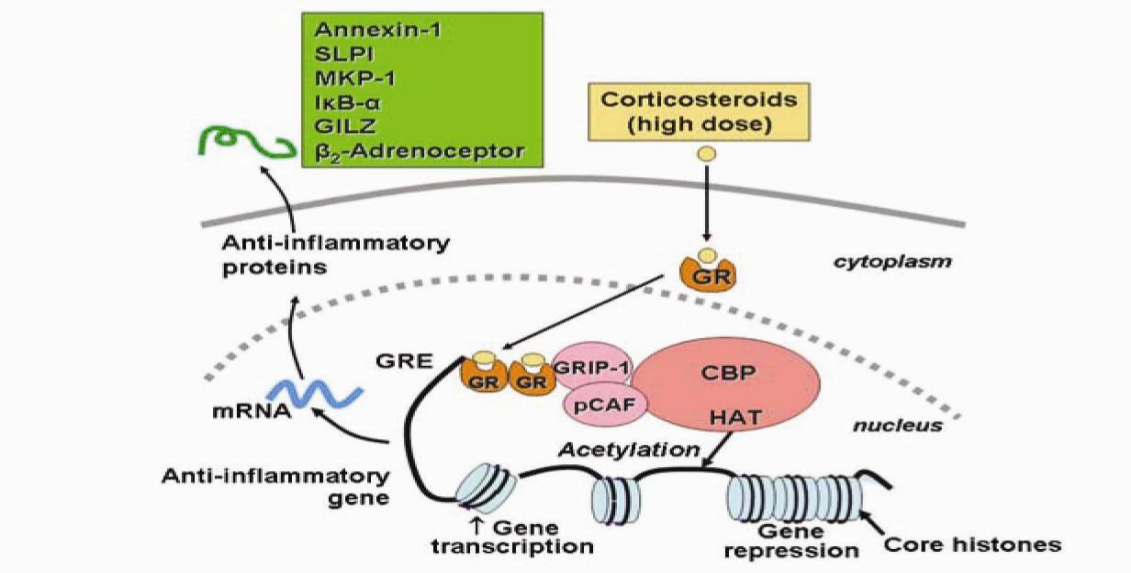


Figure 14: Corticosteroids activation of anti-inflammatory gene expression.

Anti-inflammatory gene activation

Several of the genes that are switched on by corticosteroids have anti-inflammatory effects, including annexin-1 (lipocortin-1), SLPI, interleukin-10 (IL-10) and the inhibitor of NF-kB (IkB-a). However, therapeutic doses of inhaled corticosteroids have not been shown to increase annexin-1 concentrations in bronchoalveolar lavage fluid (Hall et al., 1999) and an increase in IkB-a has not been shown in most cell types, including epithelial cells (Heck et al., 1997; Newton et al., 1998a). Corticosteroids also switch on the synthesis of two proteins that affect inflammatory signal transduction pathways, gluco- corticoid-induced leucine zipper protein (GILZ), which in-hibits both NF-kB and AP-1 (Mittelstadt & Ashwell, 2001) and MAP kinase phosphatase-1 (MKP-1), which inhibits p38 MAP kinase (Lasa et al.2002). However,

it seems unlikely that the widespread anti-inflammatory actions of cortico- steroids could be entirely explained by increased transcription of small numbers of anti-inflammatory genes, particularly as high concentrations of corticosteroids are usually required for this effect, whereas in clinical practice corticosteroids are able to suppress inflammation at low concentrations.

Side effect gene repression

Relatively little is known about the molecular mechanisms of corticosteroid side effects, such as osteoporosis, growth retardation in children, skin fragility and metabolic effects. These actions of corticosteroids are related to their endocrine effects. The systemic side effects of corticosteroids may be due to gene activation. Some insight into this has been provided by mutant GR, which do not dimerise and therefore cannot bind to GRE to switch on genes. In transgenic mice (dim) expressing these mutant GR corticosteroids show no loss in their anti-inflammatory effects and are able to suppress NF-kB-activated genes in the normal way (Reichardt et al., 2001). Several of the genes associated with side effects, including the hypothalamo–pituitary axis, bone metabolism and skin structure, appear to be regulated by interaction of GR with negative GRE sites (Ismaili & Garabedian, 2004).

Corticosteroid repression of inflammatory genes

In controlling inflammation, the major effect of corticosteroids is to inhibit the synthesis of multiple inflammatory proteins through suppression of the genes that encode them. Although this was originally believed to be through interaction of GR with negative GRE sites, these have been demonstrated on only a few genes, which do not include genes encoding inflammatory proteins (Ismaili & Garabedian, 2004).

Interaction with transcription factors

Activated GRs may interact functionally with other activated transcription factors, without the necessity of binding to DNA (nongenomic effects). Most of the inflammatory genes that are activated in asthma do not have recognisable GRE sites in their promoter regions, yet are potently repressed by cortico-steroids. There is persuasive evidence that corticosteroids inhibit the effects of proinflammatory transcription factors, such as AP-1 and NF-kB, that regulate the expression of genes

that code for many inflammatory proteins, such as cytokines, inflammatory enzymes, adhesion molecules and inflammatory receptors (Barnes & Karin, 1997; Barnes & Adcock, 1998). Activated GR can interact directly with other activated trans- cription factors by protein–protein binding, but this may be a particular feature of cells in which these genes are arti- ficially overexpressed, rather than a property of normal cells. Treatment of asthmatic patients with high doses of inhaled corticosteroids that suppress airway inflammation is not associated with any reduction in NF-kB binding to DNA, yet is able to switch off inflammatory genes, such as GM-CSF, that are regulated by NF-kB (Hart et al., 2000). This suggests that corticosteroids are more likely to be acting downstream of the binding of proinflammatory transcription factors to DNA and attention has now focused on their effects on chromatin structure and histone acetylation.

Effects on histone acetylation

Repression of genes occurs through reversal of the histone acetylation that switches on inflammatory genes (Imhof & Wolffe, 1998). Activated GR may bind to CBP or other coacti- vators directly to inhibit their HAT activity (Ito et al., 2000), thus reversing the unwinding of DNA around core histones and thereby repressing inflammatory genes. More importantly, particularly at low concentrations that are likely to be relevant therapeutically in asthma treatment, activated GR recruits HDAC2 to the activated transcriptional complex, resulting in deacetylation of hyperacetylated histones, and thus a decrease in inflammatory gene transcription (Ito et al., 2000) (Figure 4). Using a chromatin immunoprecipitation assay we have demonstrated that corticosteroids recruit HDAC2 to the

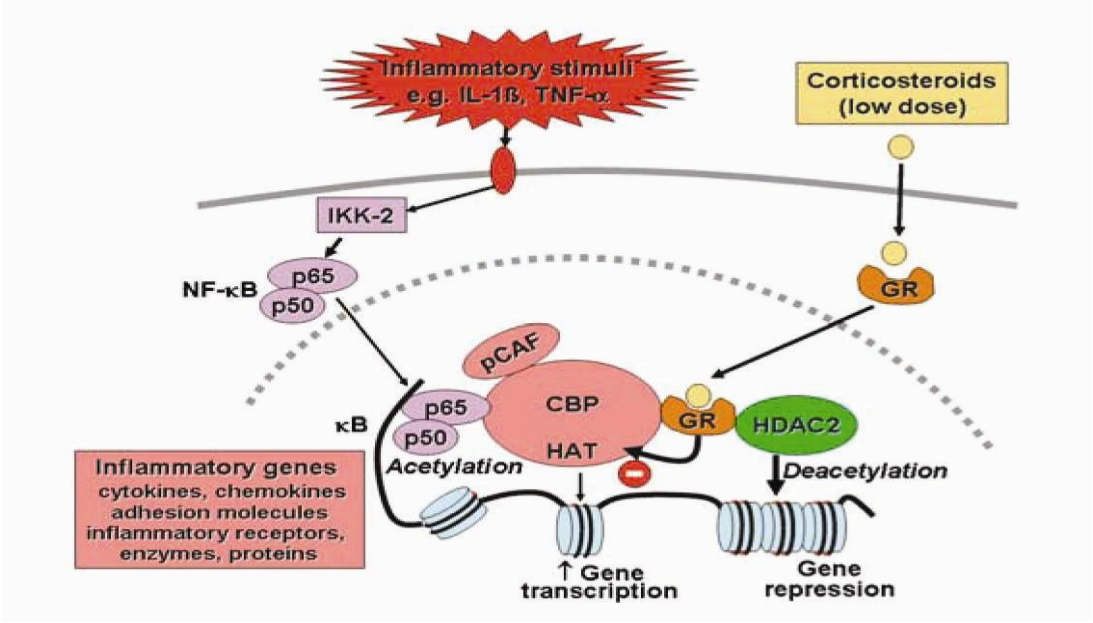


Figure 15: Corticosteroids suppression of activated inflammatory genes. Inflammatory genes are activated by inflammatory stimuli, such as IL-1b or TNF-a, resulting in activation of IKK2 (inhibitor of I-kB kinase-2), which activates the transcription factor NF-kB. A dimer of p50 and p65 NF-kB proteins translocates to the nucleus and binds to specific kB recognition sites and also to coactivators, such as CBP or pCAF, which have intrinsic HAT activity.

Other histone modifications

It has now become apparent that core histones may be modified not only by acetylation, but also by methylation, phosphorylation and ubiquitination and that these modifications may also regulate gene transcription (Berger, 2001; Peterson & Laniel, 2004). Methylation of histones, particularly histone H3, by histone methyltransferases, usually results in gene suppression (Bannister et al., 2002). The anti-inflammatory effects of corticosteroids are reduced by a methyltransferase inhibitor, 5-aza-2^0-deoxycytidine, suggesting that this may be an additional mechanism whereby corticosteroids suppressgenes (Kagoshima et al., 2001). Indeed, there may be an interaction between acetylation, methylation and phosphorylation of histones, so that the sequence of chromatin modifications (the so called 'histone code') may give specificity to expression of particular genes (Wang et al., 2004), including inflammatory genes (Wada et al., 2005; Lee et al., 2006).

GR acetylation

Nonhistone proteins are also acetylated by HATs and deacetylated by HDACs and this may be an important mecha-nism of regulating their function (Glozak et al., 2005). Several nuclear receptors, including the oestrogen and androgen receptors, may be acetylated and this affects binding of their hormones (Fu et al., 2004). We have recently demonstrated that GR is acetylated after ligand binding and that this acetylated GR translocates to the nucleus to bind to GRE sites and activate genes, such as SLPI (Ito et al., 2006). Acetylated GR is deacetylated by HDAC2 and this deacetylation is necessary before GR is able to inhibit NF-kB activation of inflammatory genes (Figure 5). The site of acetylation of GR is the lysine rich region –492–495 with the sequence KKTK, which is analogous to the acetylation sites identified on other nuclear hormone receptors. Site-directed mutagenesis of the lysine residues K494 and K495 prevents GR acetylation and reduces the activation of the SLPI gene by corticosteroids, whereas repression of NF-kB is unaffected.

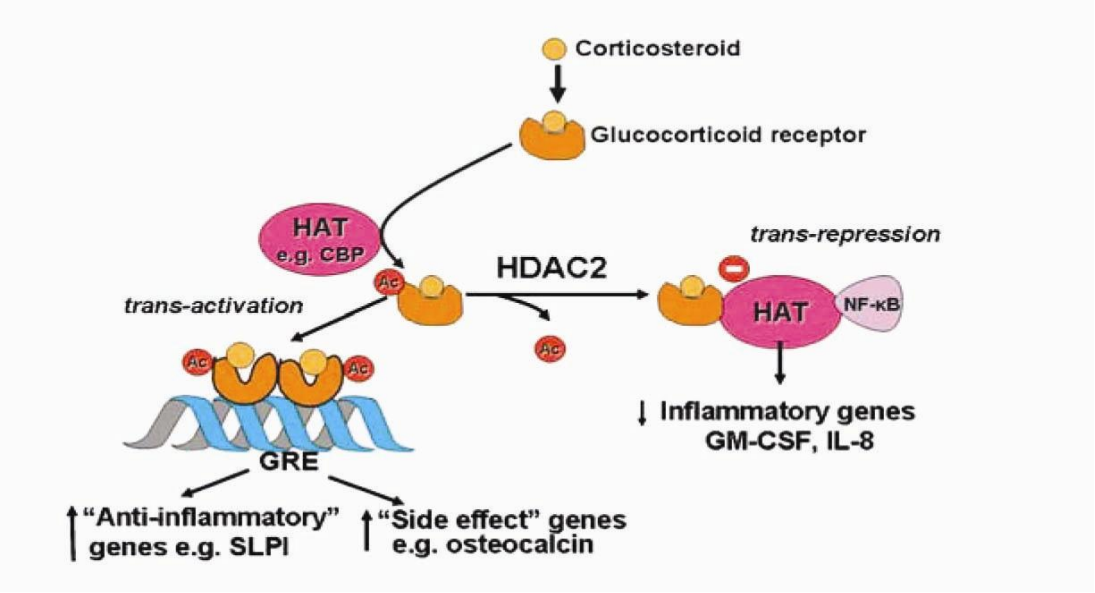


Figure 16: Acetylation of GR. Binding of a corticosteroid to GR results in its acetylation by HAT, such as CBP, and a dimmer of acetylated GR then binds to GRE to activate or suppress genes (such as side effect genes). Deacetylation of GR by HDAC2 is necessary for GR to interact with CBP and inhibit NF-kB to switch off inflammatory genes.

Nontranscriptional effects

Although most of the actions of corticosteroids are mediated by changes in transcription through chromatin remodelling, it is increasingly recognised that they

may also affect protein synthesis by reducing the stability of mRNA so that less protein is synthesised. It is increasingly recognised that several inflammatory proteins are regulated post-transcriptionally at the level of mRNA stability (Anderson et al., 2004). This may be an important anti-inflammatory mechanism as it allows corticosteroids to switch off the ongoing production of inflammatory proteins after the inflammatory gene has been activated. The stability of some inflammatory genes is determined by regulation of AU-rich elements (ARE) in the3^0-untranslated regions of the gene which interact with several ARE binding proteins, such as HuR and tristetraprolin that may stabilise mRNA (Raghavan et al., 2001; Dean et al., 2004). Some inflammatory genes, such as the genes encoding GM-CSF and cyclooxygenase-2, produce mRNA that is particularly susceptible to the action of ribonucleases that break down mRNA, thus switching off protein synthesis. Corticosteroids may have inhibitory effects on the proteins that stabilise mRNA, leading to more rapid breakdown and thus a reduction in inflammatory protein expression (Newton et al., 1998b; Bergmann et al., 2000; Newton et al., 2001). Corticosteroids do not appear to have any effect on HuR or TTP expression; however, (Bergmann et al., 2004), although a recent report indicate that corticosteroids may suppress TTP gene expression through a nongenomic mechanism, potentially destabilising certain inflammatory gene mRNAs (Jalonen et al., 2005).

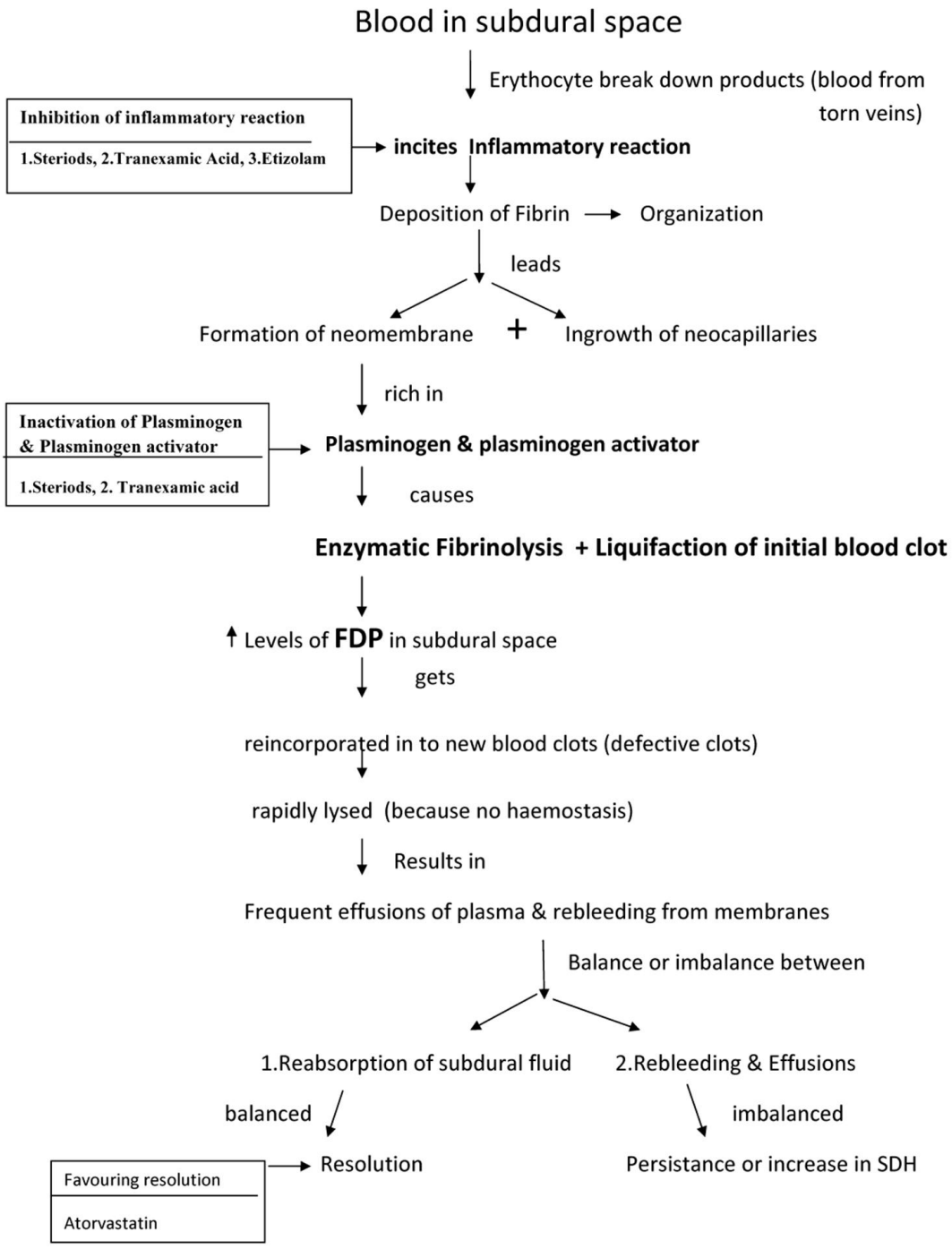


Figure 17: The cascade of events that occur in the formation of chronic subdural hematoma and drugs acting at various stages

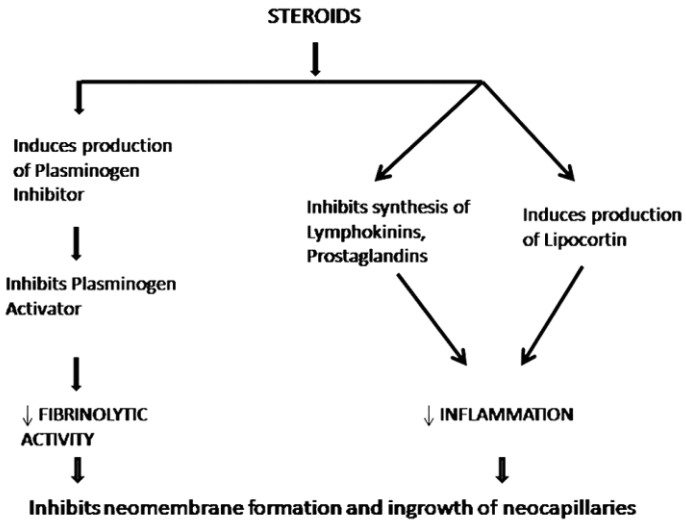


Figure 18: Mechanism of action of steroids in the treatment of chronic subdural hematoma

Baseline data collection

The following information is collected before initiation of the treatment:

Patients' characteristics: sex, age, weight, height, major medical history (including chronic alcoholism), ongoing medications affecting hemostasis (anticoagulants and platelet antiaggregants), and symptoms that led to the diagnosis of CSDH (persistent headache, repeated falls, balance disorders, attention and memory disorders, muscular weakness, motor or sensitivity disorders).

The clinical assessment includes: blood pressure meas-urement, neurological examination (Glasgow Coma Scale score, diameter and symmetry of the pupils, presence of a focal neurological deficit), functional scales (modified Rankin Scale, IADL and MMSE assessments, quality of life (SF12 scale) and comprehensive review of the overall clinical assessment score with the ASA (American Society of Anesthesiologists).

Fig 19: Study flow chart. Plasma Sodium, Potassium, and fasting glycemia/ **fasting plasma steroid

Actions	Screening Visit	Baseline Visit 1 – D0	Visit 2 – M1	Visit 3 – M3	Visit 4 – M6
Information document	√				
Clinical Examination (check the selection criteria)	√				
Written informed consent		√			
Randomization		√			
Patient characteristics		√			
Clinical Assessment					
- Neurological examination - Functional scales - Quality of life - ASA		√	√	√	√
Blood pressure measurement		√	√	√	√
Biological measurements*		√	√		
Complications related to corticosteroids			√	√	√
Surgical complications for patient who underwent surgery			√	√	√
Cerebral CT scan without contrast enhancement	√		√	√	√
Adverse events recording			√	√	√
Delivered treatment		√			
Back treatment / Observance			√		
Treatment		D1 to D21 D7*, D14*, D21*, D23** Biological measurements (laboratory to the patient's home)			

Follow-up

Patients are followed up for a period of 6 months, and are evaluated at 1, 3 and 6 months. At days 0, 7, 14 and 21 and at the 1-month visit, plasma sodium, potassium and fasting glucose are measured. Fasting plasma corti-sol at 8 a.m. is measured 2 days after the end of the treatment with corticosteroids (at day 23). Patients will undergo interval cerebral CT scans to evaluate their CSDH at the following intervals: screening visit, M1, M3 and M6 (Fig. 1). This biological surveillance allows the detection of any electrolyte or glycemic impairment that could occur with steroid treatment.

Measures

Screening phase

The screening phase takes place during the hospitalization or consultation in a neurosurgical unit during which the diagnosis of CSDH is confirmed. A standard clinical examination is performed to ensure that the patient meets the selection criteria of the study. The initial CT scan (performed onsite or in another hospital depending on the origin of the patient) completes this initial patient screening. If the patient is eligible, written informed consent from the patient or a representative (if the patient's cognitive state does not allow informed decision) is necessary before enrollment.

Treatment administered in the study

a) Surgical

Single or double twist-drill mini craniostomy over the affected hemisphere.

Patient position: Supine.

Anaesthesia: Local & mild sedation or G/A.

5-6 mm diameter manual drill to create a small burr hole.

A ventricular catheter is inserted in the subdural space.

Drainage is maintained 48-72 hours.

b) Medical Treatment

Dexamethasone Protocol.

Dexamethasone 4mg 8 hourly either oral or intravenous for 21 days.

Omeprazole 20mg 12 hourly.

Prophylaxis of thrombophlebitis

Subcutaneous enoxaparin 20-40mg per day.

Lower limbs pneumatic compression device.

Patients neurological status is checked everyday .

Patients not improving their MGS are proposed for the surgical protocol.

Dexamethasone is slowly tapered : 1mg per day every 3 days for 4 weeks.

Clinical & radiological evaluation performed after 6 weeks in OPD until complete cure.

Precautions for use

Because of the potential risk of water retention, hyperglycemia or hypokalemia, the patients will receive written dietetic advice to follow a diet with a low intake of fast-release carbohydrates and salt, and increased intake of potassium, during the treatment period. A specific dietetic form will be drawn up by a dietician before the beginning of the study. In addition to these dietetic measures, specific monitoring of plasma sodium, potassium and glucose will be carried out. Patients will also be informed of all expected steroid side effects and will be advised to contact the investigator in case of suspicion of

any adverse effects during the treatment period.

Authorized and unauthorized medicinal products Management of drugs affecting hemostasis (antiplatelet drugs, orally administered anticoagulants and heparin) will be based on the habits of the participating centers in the absence of evidence-based guidelines. Contraindications to medicinal product combinations listed in the Summary of Product Characteristics for methylprednisolone, will be complied with. In addition, clinical and/or close laboratory test monitoring will be applied whenever a potential interaction with a concomitant medicinal product exists.

In case of the failure of treatment with corticosteroids, defined by a lack of clinical improvement, clinical deterioration, immediately or after a phase of improvement, radiological progression or corticosteroid intolerance, surgical treatment should be considered. In case of persistence of the CSDH at the end of the study, its treatment will follow the centre’s normal policy.

Primary study objective

The primary objective is to evaluate the non-inferiority of primary DXM therapy versus primary BHC on func-tional outcome as expressed by modified Rankin Scale (mRS) score (Table 1) at 3 months and cost-effectiveness at 12 months in patients with symptomatic CSDH.

Secondary objectives

The secondary objectives of the study are functional and clinical outcome, expressed by mRS and Markwalder Grading Scale (MGS) scores (Table 2), respectively, at discharge, at 2 weeks, 3, 6 and 12 months and Glasgow Outcome Scale-Extended (GOSE) score (Table 3) at 3 months. Furthermore, assessment of quality of life using the Short Form – 36 Health Survey (SF-36) and Quality of Life after Brain Injury Overall Scale (QOLIBRI) will take place at 3 and 12 months and healthcare and prod-uctivity costs at 3 and 12 months. Haematoma thickness will be evaluated after 2 weeks on follow-up computed tomography (CT). Mortality will be evaluated during the first 3 and 12 months. During the total follow-up period of 12 months we will also evaluate haematoma recur-rence, complications and drug-related adverse events, failure of therapy after randomisation and requiring intervention, duration of hospital stay and overall healthcare and productivity costs.

Reference treatment

Patients randomised to the reference treatment arm are operated on preferably within the first 7 days, depending on anticoagulant or antithrombotic therapy use, severity of symptoms and discretion of the treating physician. Surgery will take place through BHC followed by insertion of a subdural drain for 2 days in line with the standard protocols in each participating hospital. Antibiotic prophylaxis is administered preoperatively. Either general or local anaesthesia will be applied. One or two 14-mm burr holes, depending on the surgeon’s discretion, are drilled over the maximum width of the haematoma. The dura mater is opened with a cruciate incision and coagulated with bipolar diathermy. The subdural collection is washed out with warm Ringer’s lactate saline, with or without a catheter. The subdural outer and inner membrane loculations, if present, can be disrupted when easily accessible via the burr holes. Whenever the saline has dispersed sufficiently a subdural drain is placed and

the wound is closed.Reoperation can be indicated when neurological deficits do not resolve, deteriorate or recur within the follow-up duration. Treatment options consist of redo burr-hole evacuation, if necessary, through another additional hole, percutaneous aspiration, craniotomy, or craniectomy.

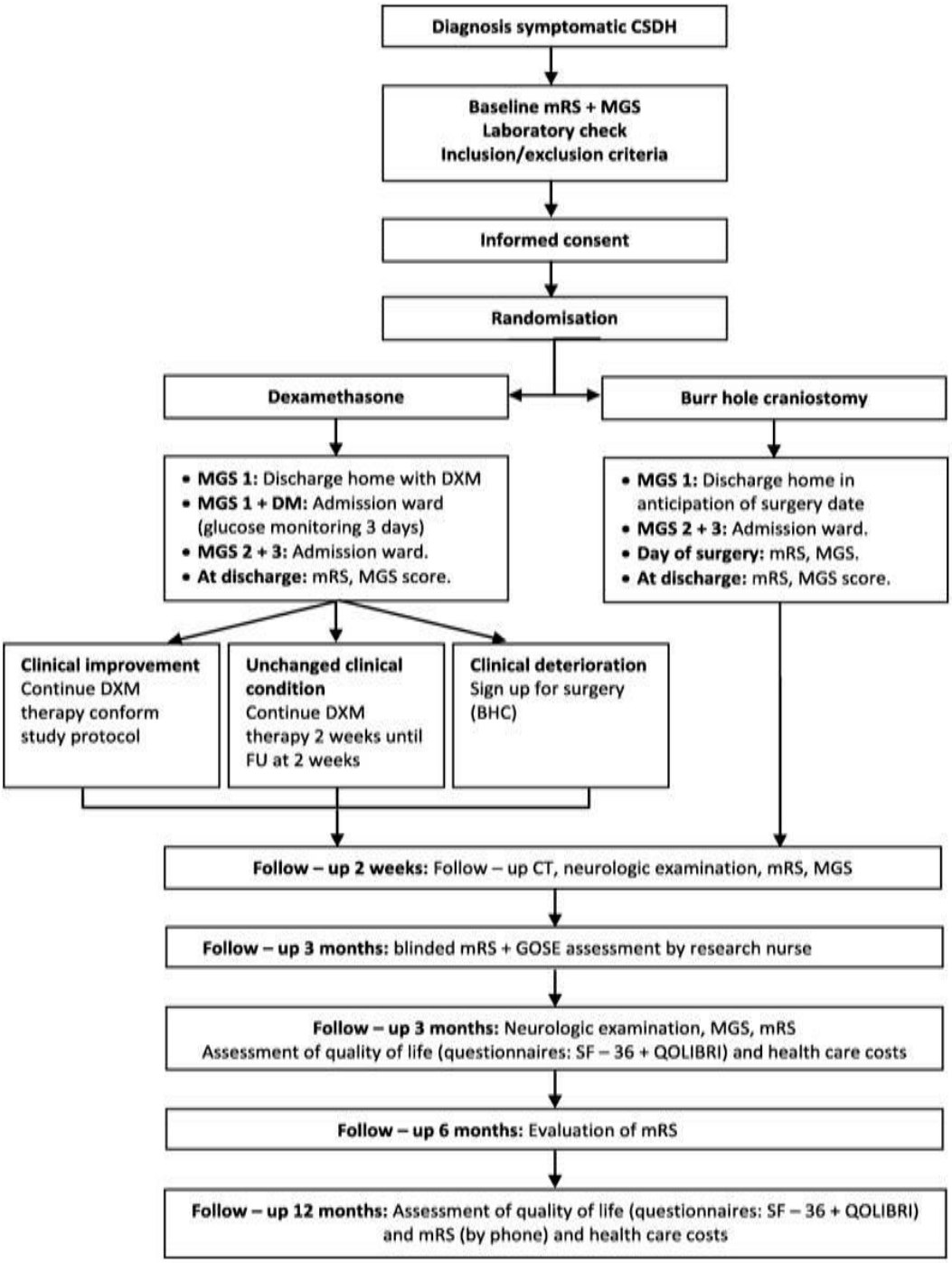


Fig 20: Flow diagram of study procedures

Inclusion criteria

Age:>18 yrs or older

Sex:Male or Female

CSDHs diagnosed:

Clinically and

Radiologically.

Clinically

Headache

Altered mental status.

Vomiting

Contra lateral limb weakness

Speech disorder

Vertigo

Seizure

Radiologically

Non-contrast CT scan of head showing chronic subdural haematoma.

CT Findings

There should be a hypodense / isodense / mixed dense area located just under the dura (Non-contrast film) with evidence of midline shifting<10 mm.

MGS grade#1-3

(MGS#The validated grading system score 0-4 for the severity of neurological symptoms).

Table 2: Modified Rankin Scales

Score	Functional status
0	No symptoms
1	No significant disability. Able to carry out all usual activities despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

Exclusion criteria

Patient with use of antithrombolytic and anticoagulant drugs.

Age less than 18 years.

CT scan showing signs of midline shifting>10mm,Uncal transtentorial herniation, acute haemorrhage or loculations or membrane formation within CSDH.

Skull fracture over the subdural haematoma.

Presence of PUD,Psychosis,active TB,acute infection & documented hypersensitivity to DXM.

Table 3: Markwalder Grading Scale

Score	Clinical status
0	Patient neurological normal
1	Patient alert and oriented; mild symptoms such as headache; absent or mild neurological deficit such as reflex asymmetry
2	Patient drowsy (defined as Glasgow Coma Scale (GCS) score: 13–14) or disoriented with variable neurological deficit, such as hemiparesis
3	Patient stuporous (defined as GCS 9–12) but responding appropriately to noxious stimuli; severe focal signs such as hemiplegia
4	Patient comatose (GCS 8 or lower) with absent motor responses to painful stimuli; decerebrate or decorticate posturing

Table 4: Glasgow Outcome Scale-Extended

Score	Category
1	Death
2	Vegetative state
3	Severe disability, lower
4	Severe disability, upper
5	Moderate disability, lower
6	Moderate disability, upper
7	Good recovery, lower
8	Good recovery, upper

Participant timeline

The time schedule in Fig. 21 describes all study processes, assessments and interventions. The flow diagram (Fig.2) displays the main study procedures, including follow-up evaluations. In summary, study patients will be evaluated at presen-tation (baseline), during their hospital stay, at discharge and during the follow-up period at 2 weeks, 3 months, 6 months and 12 months. At 2 weeks (after initiation of the study treatment) pa-tients will be evaluated by neurological examination combined with a follow-up CT scan at the outpatient clinic or ward and at 3 months at the outpatient clinic. A mRS-certified research nurse, blinded for treatment allocation, will evaluate the primary outcome (mRS score) at 3 months by phone. At 3 and 12 months, patients will receive questionnaires on quality of life. Additionally, an evaluation of mRS score will take place by phone at 3, 6 and 12 months. Healthcare and productivity costs will be evaluated at 3 and 12 months. We expect to complete patient inclusion in 3 years. The estimated duration of the study (including follow-up) will be 4 years.

Participant timeline

The time schedule in Fig 21: Describes all study processes, assessments and interventions including follow – up evaluations

Study procedure	Initial screening	During admission	Day of surgery	Day 1-2 post surgery	At discharge	FU (2 weeks)	FU (3 months)	FU (6 months)	FU (12 months)
Medical history	*								
Demographics	*								
Concomitant medications	*	*	*		*				
Neurological examination	*	*(OD[1])	*		*	*	*		
Vital parameters	*	*(OD[4])			*				
CT - scan	*		*			*			
Laboratory evaluation	*	*	*	*					
Glucose monitoring	*	*							
Informed consent	*								
MGS	*		*		*	*	*	*	*
mRS	*				*	*	*	*	*
GOSE	*						*		
Quality of life (SF-36, QOLIBRI)	*						*		*
Costs	*						*		*
Complications		*			*	*	*	*	*
Adverse events		*			*	*	*	*	*
Serious adverse events		*			*	*	*	*	*
Mortality		*			*	*	*	*	*

Concomitant care

All included patients will otherwise receive routine standard of care. Patients with mild neurological deficits (MGS grade 1) on admission can be discharged home in anticipation of the planned BHC or awaiting the effect of DXM therapy. However, in MGS grade 1 patients with known diabetes mellitus with HbA1C < 64 mmol/ mol randomised for DXM therapy, monitoring for blood glucose levels is necessary during the first 3 days after treatment initiation. Glucose monitoring can take place clinically during admission or if possible at the nursing home. Patients with MGS grade 2–3 (in either arm) re-main in hospital until the treating physician judges the clinical situation safe for discharge.

During admission neurological investigations and vital parameters are recorded daily. Low-molecular-weight heparin will be applied in both patient groups as thrombosis prophylaxis if the patient is not optimally mobile. Patients will receive physiotherapy, speech the-rapy or rehabilitation consultation if deemed necessary.

Anticoagulant or antithrombotic therapy oral anti-coagulant or antithrombotic therapy will be discontinued in both study arms from the moment of randomisation to prevent haematoma growth and to avoid interference with planned surgery. In case of vitamin K antagonist therapy the international normalised ratio is cor-rected to ≤ 1.5 through the administration of vitamin K and/or prothrombin complex concentrate, as is the current practice. For patients using platelet-aggregation-in-hibitor therapy, surgery is preferably planned 7 days after discontinuation of therapy, if allowed by the clinical condi-tion. At the discretion of the surgeon, earlier intervention is allowed if deemed clinically necessary. The reason for early surgery has to be recorded in the case report form. Non-vitamin-K oral anticoagulants are discon-tinued at least 1 day prior to surgery.

Any anticoagulant or antithrombotic therapy can be resumed 2 weeks after the initiation of DXM therapy or surgery following a follow-up CT without signs of CSDH recurrence, recent-onset haematoma or unchanged mass effect with midline shift compared to the initial CT at randomisation. Partial resolution of CSDH at this stage without recent haematoma is not a contraindication for resumption. For absolute indications (e.g. mechanic car-diac valve) earlier resumption or bridging of therapy

within these 14 days is allowed. Any reason for early resumption has to be recorded in the CRF. Subgroup analyses will be performed to evaluate the effect of anti-coagulant therapy in both groups.

Outcomes

Primary outcome measures

The primary endpoints are the functional outcome, expressed by mRS, at 3 months after start of study treat-ment and cost-effectiveness at 12 months.

Secondary outcome measures

Secondary outcomes include: functional and clinical out-come, expressed by mRS and MGS scores, respectively, at discharge, at 2 weeks, at 3, 6 and 12 months after start of study treatment. We will also determine a utility-weighted mRS at 3 months. The GOSE score will be assessed at 3 months, quality of life (expressed by SF-36 and QOLIBRI) at 3 and 12 months, cost-effectiveness at 3 and 12 months and haematoma thickness at 2 weeks. During the first 12 months, we will evaluate haematoma recurrence (defined as recurrence of symptoms and neurological signs after initial improvement with persis-tence, recurrence or increase of CSDH on follow-up CT), failure of therapy after randomisation and requiring inter-vention, complications and drug-related adverse events, duration of hospital stay and healthcare and productivity costs in both patient groups. Finally, we will evaluate mortality during the first 3 and 12 months.

Adverse events and serious adverse events

Adverse events are defined as any undesirable event occurring to a patient during the study, whether or not considered related to DXM therapy or surgery. All adverse events reported spontaneously by the patient or observed by the investigator or staff will be recorded. A SAE is any untoward medical occurrence or effect that results in death; is life-threatening (at the time of the event); requires hospitalisation or prolongation of exis-ting inpatients' hospitalisation; results in persistent or significant disability or incapacity or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention, but could have been based upon appropriate judgement by the investigator. SAEs are reported by the

investigators in participating centres to the coordinating investigator. SAEs will be reported through the web portal Toetsin-gOnline to the accredited Medical Ethics Committee that approved the protocol.

Treatment

Without mass effect on imaging studies and no neurological symptoms or signs, CSDH can be followed up with serial scans and may resolve spontaneously. Liquefied CSDH can be treated with drainage through 1 - 2 burrholes. A non-liquefied CSDH cannot be decompressed adequately by burrholes and must be done by craniotomy. Bilateral CSDH should be drained from both sides.[16] Medical treatment includes supportive management and proper resuscitation of the patients.

Dexamethasone protocol

It consists in the administration of 4 mg of dexamethasone every eight hours, either oral or intravenous; bed rest; oral diet if possible (or through nasogastric tube) or fluid reposition, depending on the level of consciousness; omeprazole (20 mg per day); and prophylaxis of thrombophlebitis with either subcutaneous enoxaparin (20-40 mg/ day) and/or lower-limbs pneumatic compression device. Patient's neurological status is checked every day and the effectiveness of corticotherapy is re-evaluated after 48-72 hours. Those patients not improving their MGS are proposed for the Surgical Protocol. The rest are either allowed to ambulate or discharged and dexamethasone is slowly tapered (reducing 1 mg per day every three days) until complete withdrawal. Clinical and radiological evaluation is performed after 6 weeks (in the Outpatient Office) and further on until complete cure or clinical-radiological stabilization.

Surgical protocol

We advocate for the performance of a single (or double, in bilateral CSHs) *twist-drill* mini-craniostomy over the affected hemisphere, preferably in the frontal region. The procedure is done with the patient supine under local anaesthesia and mild sedation. We use a 5-6 mm diameter manual drill intending to create a small burr hole as parallel as possible to the inner table of the skull in order to minimize the risk of brain penetration. A ventricular catheter is inserted in the subdural space and a moderate quantity of liquid is allowed to exit until the initial overpressure is relieved. The

catheter is connected to a collecting device located at least 20-30 cm below the patient's head, letting the fluid out *drop-by-drop*. The bloody CSF outflow rate is thus controlled intending to avoid pneumocephalus or contralateral haematomas. No subdural irrigation is performed. The drainage is maintained 48-72 hours. Surgical time rarely exceeds 10-15 minutes. Antimicrobial prophylaxis is maintained as long as the catheter remains inserted (intravenous Cephazolin 2gr/8h or Vancomycin 1g/12h). Clinical re-evaluation is done after drainage withdrawal. Patients not clearly improving after drainage are initiated on dexamethasone as an adjuvant therapy. Some cases needed a second drainage due to re-accumulation of liquid and very few underwent craniotomy and membranectomy. The latter technique was reserved for unresponsive and rapidly deteriorating patients. The same follow up protocol as in medical patients applies in this group.

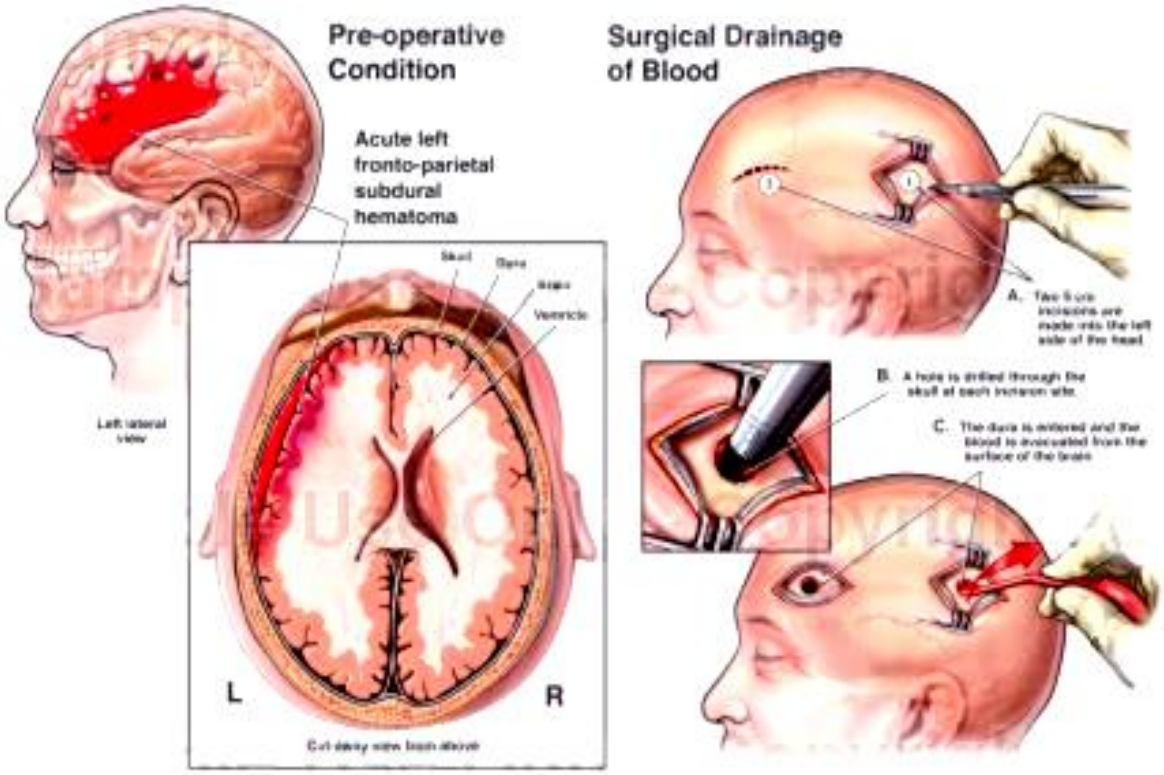


Fig 22: Burr hole drainage

Outcome and prognosis

Medical or surgical complications occur in ±19% of patients who have their haematomas drained surgically. Medical complications include seizures, aspiration pneumonia and other infections. The outcome after drainage of CSDH correlates with the preoperative neurological state. Early diagnosis before significant neurological deterioration correlates with a favorable prognosis. The mortality rate within 30 days of surgery is 3.2- 6.5%.[16] Eighty percent of patients will recover to their level of function existing prior to presentation.

Chronic subdural haematoma

Chronic subdural haematoma is collection of blood between the dura and arachnoid usually caused by tear of bridging veins.[15] Some literature however suggests it occupies intradural space as a result of disruption of dural border cell layer from deep patchy meninges.[21] Whereas aetiological factors for acute subdural haematoma are well known; that is, parenchymal laceration that mainly affects fronto-temporal regions and tear from bridging veins both of which result from major head trauma and less commonly minor trauma in coagulopathic patients; 50% of chronic subdural have no identifiable cause.[21] However they are commoner and larger in elderly who have cerebral atrophy with consequent increased length of bridging veins which are also brittle.[22] In some studies however, like in a series of 21 cases of spontaneous subdural haematoma, underlying causes included hypertension (7 cases) AVM, neoplasm, infection, alcoholism and innocuous insult. The aetiological factors in our local setup however was largely unknown. Although the risk factors for patients presenting in our hospital is unknown, studies done elsewhere have shown the following to be some of the risk factors. Extreme of ages- infants have large dural space hence are more predisposed to interhemspheric SDH. They are also at risk of child abuse. The elderly on the other hand have brain atrophy same as patients with degenerative neurological disease. Trauma as a predisposing condition has been diversely appreciated in literature. Lee et al. (1998) noted in his series that acute subdural haematoma as a result of major head trauma turned to CSDH in 3%-6% of cases. However, minor head insult has been confirmed by different author[23] to be a major predisposing factor. Stroobandt[24], in his study of 100 patients, found it be as high as 80%, compared to taking aspirin (16%), coagulopathy (6%) and ethylism(11%). Patients who are prone

to minor repeated trauma include those with convulsive disorders, hemiparetic patients (post CVA)or alcoholics(in addition to hypoprothrombinaemia).[25] Other known risk factors include low CSF pressure conditions (for example after a lumbar puncture or after insertion of Ventriculo peritoneal shunt) and arachnoid cysts, especially in children[26] Patient on anticoagulation have increased risk of up to 7 times in males and 26 times in females.[27] The incidence of CSDH in this coagulopathic patients ranged from 10% to as high as 42% as found by different authors 10%[28], Hardes et al.[29] 18%, Reymond et al. 26%[30] while Koniq et al. (1983) found 42% coagulation disorders in his series of 114 patients of whom 13% were alcoholic, 8% on salicylate with accompanying platelet aggregation abnormality, 5% on warfarin and 6% had hematological/oncological diseases.[27] In terms of assessment of coagulopathy, INR was found to be the best indicator in coagulation profile that included complete blood count, liver function tests, prothrombin time, activated partial thromboblastin time. platelet count and fibrinogen level. In a multivariate analysis of risk factors in oral anticoagulation related to intracranial haemorrhage carried out by Berwerts and Webster[31] ,hypertension, INR >4.5 and duration of anticoagulation were found to be significant predisposing factors. More ever incidence of CSDH in patients on warfarin was found to be between 21%-36% .This rate was even higher (75%) for those with spontaneous CSDH.[30] For this reason Doublis et al. (1999) advices, stopping the warfarin with correction of INR by use of fresh frozen plasma (100ml/kg) and factor K concentrate to achieve INR of 1.5 or less[32] before surgery and restarting it on third post operative day to achieve therapeutic INR of 2-3 for most conditions except for mechanical heart disease that requires higher INR of 3-4 4,[33] Clinical presentation of chronic subdural haematoma is varied. The common presentation in our local setup was largely unknown. However, common clinical presentations in the literature include presenting complaints of: Confusion/disorientation/personality changes; Headache which could be constant or fluctuating and associated with nausea or vomiting, blurring of vision, gaze palsy or ophthalmoplegia; Seizures which are mostly focal but could also be generalized; Dysphasia or slurred speech; Ataxia/inability to walk or motor weakness; Low level of consciousness or fluctuating level of consciousness (Transient ischemic like syndrome) and a history of recent head injury. And on examination, patient will often have low level of consciousness like confusion, Drowsiness, signs of head trauma e.g. scalp laceration/bruises, Motor weakness with or without Pupillary defect

and specifically for interhemspheric subdural haematomas, patient will have a constellation of paresis, focal seizures, gait ataxia, dementia, language disturbance and occulomotor palsy. In terms of imagiging, CT Scan of the head is the preferred imaging modality for acute subdural haematomas and usually shows a crescent shaped hyper dense lesion crossing suture lines. Normura and colleagues[34] divided chronic subdural into five types based on CT scan findings as follows;

High density

Mixed density they were found to be active with high tendency to rebleed

Layering type

Isodense type

Low dense type: they were found to be most clinically stable

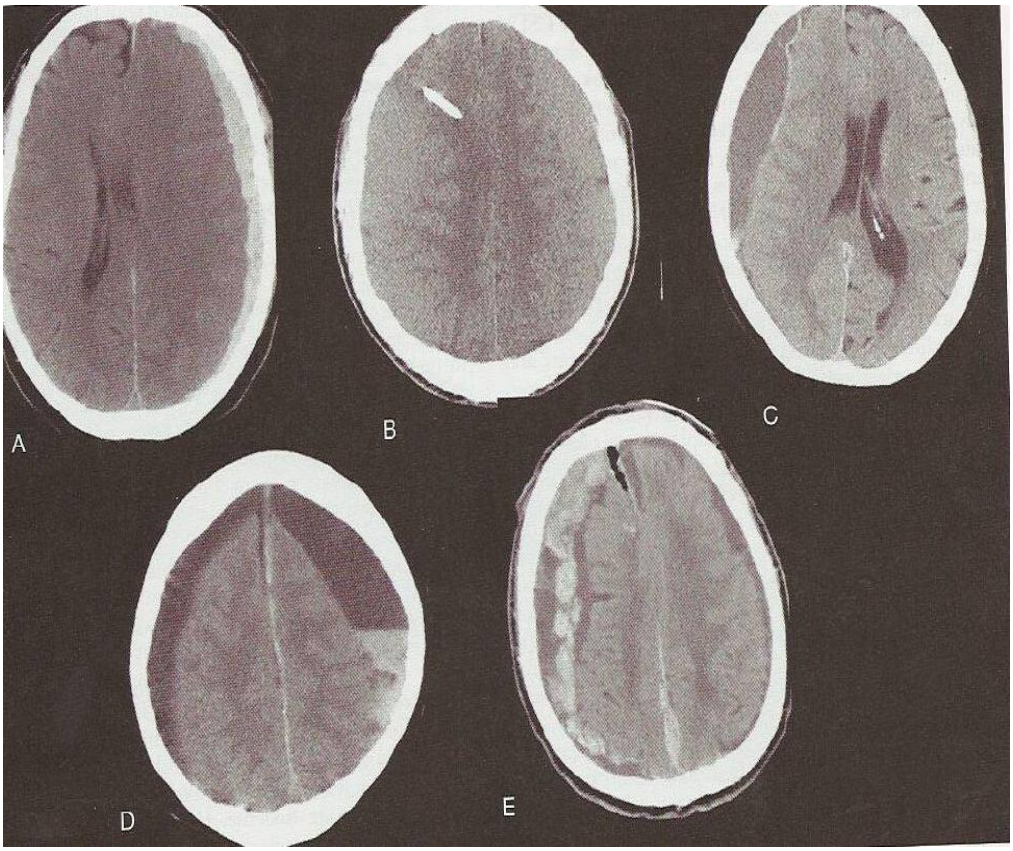


Figure 23: CT Scan findings as outlined by Normura *et al.*[34]

A. hyperdense. B. isodense C. low density D. mixed density E. layering type MRI is more useful after 48 hours to asses extent of brain injury, the intradural location, its multiple compartment and the probable age of the haematoma.CT scan may also not depict well the 25% of cases that are isodense to brain or severe cerebral atrophy that can leave prominent subarachnoid space.

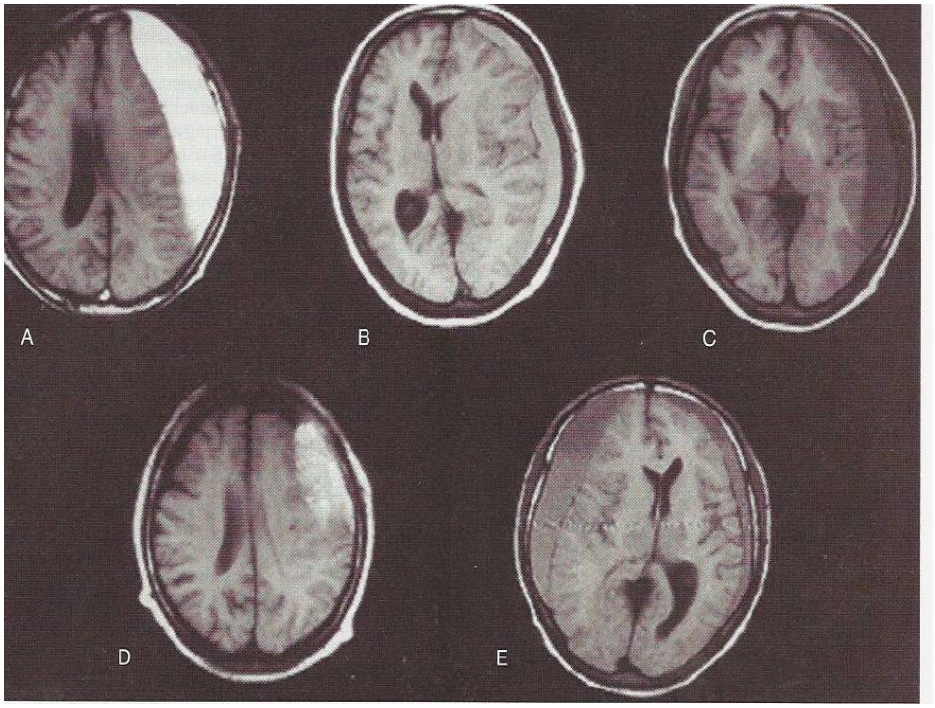


Figure 24: MRI findings

Based on this MRI findings, Tsutsumi et al studied 230 CSDH patient and classified them into 5 groups based on T1 findings (hyper; hyper/iso, iso, iso/hypo and hypointensity). Recurrence was found to be lowest in hyper intense group (3.4%) compared to the rest (11.6%).[35] Due to the high cost of MRI, it is not readily available in our local setup unless in special circumstances where CT scan head is not diagnostic. In our study, we sought to know the percentage of the patient with chronic subdural haematoma that would need MRI to confirm the diagnosis.

As pertains to the management of this condition, there is no uniform agreement on best method of treatment of chronic subdural haematoma.[29] Surgical options include:

Two standard burr holes placed on same line as trauma flap followed by saline irrigation using soft Jacques catheter.

A large burr hole (2.5cm) i.e. sub temporal craniectomy with gel foam placed into the opening. This allows content to drain into sub temporal muscle

Single burr hole with subgaleal drain left in situ for 24-48 hrs when the output is negligible. In some studies, it has been shown that the drain reduced recurrence rates from 19% to 10%.[36]

Twist drill craniostomy (5 mm) with subdural drainage. This however has high recurrence rates than the conventional burrhole. The advantage of twist drill though is that it decompresses the subdural space slowly; thus avoiding rapid pressure release that can lead to cortical hyperemia or even intracerebral hemorrhage. The ventricular catheter is usually placed into subdural space and then connected to reservoir placed 20 cm below head and patient is instructed to lie flat post operatively for 24-48 hrs.

Comparing the three main methods that are usually employed in management of this condition (ie 1,3 an 4 above) in a study done by William et al.[37] ,they found out that the patients who underwent twist-drill and closed system drainage, 43% of them had smaller lesions on follow-up CT scans, as compared with 74% of those who underwent the burr-hole only procedure, and 65% with burr-holes with drains. Clinical outcome showed that 64% of twist-drill and CSD patients deteriorated as compared with 16% of those with burr-hole only and 7% with burr-holes and CSDs. Sixty-four per cent of twist-drill patients required repeat evacuations as compared with 11% of those with burr-holes only, and 7% with burr-holes plus drains. Hospitalization days was also longer as found out by Okada Y et al.[38] 14.1 days in the drainage group and 25.5 days in the irrigation group4.Twist drill however had better outcome when CSD was combined with suction reservoir and outcome was actually comparable to burr hole drainage in terms of length of hospitalization, recurrence rate, mortality, and neurological recovery and better still, a repeat CT scan done at two months showed complete regression of subdural effusion in 66.6% of cases in the TDC group compared to 31.8% in the BHC group ($P<0.05$).[39]

According to Emastus R.I burr hole craniostomy with closed-system drainage should be the method of choice for the initial treatment of CSDH, even in cases with preoperative detection of neomembranes. Craniotomy should be carried out only in patients with reaccumulating haematoma or residual haematoma membranes, which prevents expansion of the brain.[40] Even then, according to Lee J's[41] retrospective study which was performed on 172 patients with CSDH, comparing the efficacy of three different primary surgical methods; rate of reoperation in the group of burr-hole

drainage was 16%, slightly lower than in partial membranectomy with enlarged craniectomy (18%) or extended craniotomy(23%).This is reaffirmed by literature review done by Wigel et al.[42] where although there was no article that provided class I evidence, Six articles met criteria for class II evidence and the remainder provided class III evidence. Evaluation of these results showed that twist drill and burr hole craniostomy were safer than craniotomy; and although burr hole craniostomy and craniotomy were the most effective procedures; burr hole craniostomy had the best cure to complication ratio (type C recommendation). Irrigation lowered the risk of recurrence in twist drill craniostomy and did not increase the risk of infection (type C recommendation). Drainage reduced the risk of recurrence in burr hole and twist drill craniostomy, and the use of a drain did not increase the risk of infection (type C recommendation). However Burr hole craniostomy appeared to be more effective in treating recurrent haematomas than twist drill craniostomy, and craniotomy was considered the treatment of last choice for recurrences (type C recommendation).

For the burr hole craniostomy, the number of bur holes is an independent predictor of recurrence. This is according to a retrospective study done by Taussky P consisting of 97 haematoma. 63 (65%) haematomas were treated with two burr holes, whereas 34 (35%) were treated with one burr hole. Patients with one burr hole had a statistically significant ($p < 0.05$) higher recurrence rate (29 vs. 5%), longer average hospitalization length (11 vs. 9 days) and higher wound infection rate (9% vs. 0%).[43]

The less invasive surgical technique is bedside percutaneous subdural tapping with spontaneous haematoma efflux after twist drill craniostomy under local anaesthesia.A prospective study done on 118 adult patients, 99 with unilateral and 19 with bilateral CSDH by Reinges MH[44] had a mean number of subdural tappings of 3.2. Ninety two of the patients with unilateral CSDH were successfully treated by up to five subdural tappings and 95% of the patients with bilateral CSDH up to 10 subdural tappings. The mean duration of inpatient treatment was 12 days. The only significant predictor for failure of the described treatment protocol was septation visible on preoperative CT. Thus, it can be recommended in all patients as a first and minimally invasive therapy, especially in patients with a poor general condition. However, Patients with septation visible on preoperative CT should be excluded from this form of treatment. Post operative complication of CSDH include recurrence, tension pneumocephalus,

seizures, empyema, intracranial haemorrhage, transient post operative clinical detoriation and death.

Symptomatic recurrence is appearance of neurological signs and symptoms with radiological increase in volume of CSDH within weeks or months that is different from residual collections. Infact according to one study, persistent fluid was seen in 78% of cases on post op day 10; 15% day 40 and up to six months for complete resolution. Hence there is no treatment for recurrence unless CT Scan done at 20 days post operative show increase in size of haematoma and there is no clinical recovery or there is detoriation36.

Recurrence rates vary between 3.7-21.5%.[6] Recurrence is higher in elderly patients50as found by Stroobandt et al.[24]. This could be attributed to failure or extreme slowness of brain expansion seen in elderly patient. According to Normura et al.[34] and Nakaguchi et al.[45] the separated type/layering type are associated with higher recurrence.26,53 In fact Nomura et al.[34] analyzed the concentrations of fibrinogen, fibrin monomer, and d-dimer in patients with “layering-type” CSDH and reported that the layering type of CSDH is active, has a high tendency to rebleed, and exhibits hyperfibrinolytic activity. This non homogeneity occurs as part of intermittent cyclic process of haemorrhage originating from external membrane capillaries favored by FDPs or as a consequence of new trauma.[46]

Other factors predisposing to high recurrence include: coagulopathy, intracranial hypotension, intracranial air on post CT scan, alcoholism, seizures, cerebral atrophy, CSF shunts and bilateral surgery. Placing patient in supine or upright position have no influence on recurrence rate. Diabetes Mellitus is associated with low recurrence rate probably due to high osmotic pressure and increased platelet aggregation. This hyper viscosity diminishes rebleed rate.[47] According to Stansic et al.[48], the surgical factors, type of anaesthesia, site of initial surgery, use of drainage, duration and volume of drainage, post operative massive air collection and surgical experience of operators related to the initial procedure did not influence PR rates at significant levels.[48] Tension pneumocephalus as apost operative complication is usually rare with rates varying between 1-2%. The overall incidence of post-CSDH seizures varies from 2.3 to 17% 62 with a reported incidence of post-operative seizures between 1.0 and 23.4%.[49] Although one study has verified a significant increase in morbidity and

mortality associated with respiratory complications and status epilepticus in patients with new onset seizures after CSDH, the efficacy of prophylactic anti-convulsive medication has been debated and its use is not consensual. Lower mean GCS on admission is independently predictive of seizures, most of which occur within the first three months after CSDH70 and in fact a decrease of one mean GCS increased the seizure rate by 21.6% according to a study done by Yu-Hua Huang et al.[50] Since the incidence of seizures vary widely in literature,we will seek to establish the true incidence, both preoperatively and post operatively and the likely risk factors. Infection of subdural space is rare and may also occur with untreated CSDH. We will determine the incidence of subdural space infection, the common pathogens and the possible predisposing factors in our study. Intracerebral haemorrhage on the other hand is common in elderly (over 75yrs). It is thought to be as a result of rapid decompression leading to cortical hyperemia with subsequent risk of spontaneous intracerebral bleed.[51] Incidence varies between 0.7-7%. It is associated with high mortality.(1/3 die and another 1/3 are severely disabled).Overall Mortality varies in literature from 1-8%. Age, general condition and neurological grading are contributing causes. In this study we wanted to establish the mortality in our setup, and whether age, general condition and neurological status played a significant role. Another rare complication is post operative clinical detoriation, for example development of aphasia or hemi paresis but with negative findings on imaging. These kind of patient however, are known to responds well to short term treatment with mannitol.[40]

Conservative treatment of chronic subdural haematoma

Chronic subdural haematoma, one of the most common neurosurgical entities, occurs typically in elderly patients. The incidence is expected to double by the year 2030, owing to the continuous aging of the population. Surgery is usually the treatment of choice, but conservative treatment may be a good alternative in some situations.[52]

The incidence in people 70 years of age and older is estimated at 58/100 000 persons a year.[53] In 41% of the cases, patients are treated with oral anticoagulation or antiplatelet therapy at the time of diagnosis.[54] Since the incidence is expected to double by the year 2030, owing to the continuous aging of the population, there is a need for evidence-based management guidelines for both general and specialised

healthcare practitioners.[55] Surgical treatment is considered the gold standard for symptomatic CSDH, but may become complex because most of the patients are advanced in age and/or are being treated with anticoagulants. Even though the outcome of surgical treatment is considered good, conservative treatment may be highly valuable in some situations. An understanding of the pathophysiology is crucial for the development of medical agents in order to treat CSDHs conservatively. In healthy individuals, the subdural space is a virtual space.[55] A layer of dural border cells with enlarged extracellular space containing bridging veins is tethered between the dura mater and the arachnoid mater.[56] In individuals with brain atrophy (e.g., elderly, alcoholics), the bridging veins are stretched since the arachnoid is separated from the dura mater. These stretched veins can be easily torn, typically as a result of minor trauma, leading to acute bleeding into the virtual subdural space. Thereafter, fibrin deposition and fibrinolytic organisation occurs, and the blood in the subdural space triggers inflammation.[57] After weeks, neomembrane with fragile neocapillaries is formed, typically leading to further microbleeding and the maintenance or enlargement of the SDH. Other factors influencing the enlargement of the SDH are: fragility of the neocapillaries,[56] acceleration of fibrinolysis, high concentration of fibrin degradation products[58] and high concentrations of vascular endothelial growth factor in the subdural space. Chronic SDH is also described as a circumscribed chronic self-perpetuating inflammatory disorder. Stanisic et al.[48] showed significantly higher levels of proinflammatory mediators (interleukin-2 receptor, and interleukins 5, 6 and 7) and anti-inflammatory mediators in the CSDH fluid compared with systemic levels, as well as a higher ratio of pro- to anti-inflammatory mediators. The contact between CSDH fluid and the dural border cells seems to evoke a local aseptic inflammatory and inflammation-induced angiogenic reaction. This angiogenic reaction leads to the formation of neomembranes that cause repeated microbleeds into the haematoma cavity. Consequently, CSDH may be considered as an angiogenic disease, where inflammatory phenomena play a major role. A clinical classification, namely the Markwalder grading score, might help to decide which therapy modality might be more appropriate. However, no consensus exists about the best treatment for each grade and the treatment modality that should be chosen individually for each patient. Symptomatic patients with a confirmed radiological appearance of a haematoma are usually treated surgically, whereas patients with asymptomatic

haematomas and small non-space-occupying haematomas can be managed conservatively with a medical agent or through careful observation.[59]

Relevant studies

The first study evaluating the nonsurgical treatment of CSDH with corticosteroids was performed in 1974 by Bender et al.[60]. This study, from the era before CT (diagnosis was based on angiography), compared medical treatment (n = 75; prednisone 60 mg orally for a few days, thereafter reduction of dose by 10 mg every 3 days) to medical and surgical treatment (n=22) and surgical treatment only (n = 88). Of the 75 patients treated medically, 22 were considered as medical failure and therefore underwent operation. The medically treated group showed no mortality and poor outcome in two cases, whereas in the surgical group 12 patients died and 7 had poor outcome. Based on these results the authors recommend surgery as the first choice of treatment in comatose or progressively worsening patients, whereas treatment with corticosteroids should be started in all other patients and when the response is good, should remain the only treatment (type C recommendation). A retrospective study by Pichert et al.[61] in 56 patients treated medically with corticosteroids (regimen unknown) showed a favourable outcome in 83%, whereas 8 patients eventually required surgical drainage. They concluded that conservative treatment with corticosteroids can be recommended in patients without distinct focal symptoms and nonsoporose or noncomatose patients (type C recommendation). In 2005, a prospective cohort study of 112 patients with CSDH was conducted, in which 26 patients were treated with corticosteroids (dexamethasone 4 mg four times a day for 21 days), 69 patients were treated with burr hole drainage and postoperative corticosteroids, 13 patients had with surgical drainage alone, and 4 patients received neither surgery nor corticosteroids.[62] In the corticosteroid group, one patient (4%) required burr hole drainage after 1 month and in surgical group recurrence was seen in three patients (4%), with no significant difference between the groups. In the group without any treatment, two out of four patients ultimately required surgical drainage. Hospitalisation time, outcome and mortality were comparable in the steroid group, the steroid plus surgical drainage group, and the surgical drainage only group. Significant steroid-related complications were not reported, and two diabetic patients treated with steroids required additional insulin therapy for optimal diabetic control only during

the treatment period. The authors conclude that corticosteroids might be a valid alternative for patients with CSDH not suitable for surgical drainage. However, large randomised studies are needed to confirm these suggestions (type C recommendation). In 2009, Delgado-López et al.[1] compared, in a retrospective manner, a conservative regimen of corticosteroids (patients with MGS 0–2, dexamethasone 4 mg every 8 hours for 48–72 hours, if patient showed improvement discharge and dose reduction by 1 mg/day every 3 days) with a surgical regimen with twist drill craniostomy (patients with MGS 3–4). Patients treated with steroids showed a good outcome in 96% of the cases, whereas 93% of patients treated operatively showed favourable outcome. The median hospital stay was shorter in the dexamethasone group (6 vs 8 days). Medical complications occurred in 27% of the patients treated with corticosteroids, most commonly mild hyperglycaemia and nosocomial infections. In two thirds of the patients treated conservatively surgery was avoided. The authors concluded that corticosteroids were effective in 67% of the cases and are therefore a safe and feasible conservative treatment for patients presenting with CSDH and a MGS of 0–2 (type C recommendation).[1] A meta-analysis by Almenaver et al. showed no significant difference in recurrence rate, morbidity and mortality for patients treated with corticosteroids when compared with surgical treatment (type B recommendation).[63] The authors commented, however, that these findings should be interpreted cautiously since the number of studies included was small and further studies are warranted. Lastly, a recent prospective study evaluated the role of corticosteroids (dexamethasone 4 mg every 8 hours for 3 days, if successful dose tapering for 4 weeks) as a medical treatment for cSDH in 26 patients.[64]

In 15 cases (10 patients after 3 days, 5 patients at 3–6 weeks) burr-hole drainage was eventually needed, whereas the remaining 11 patients were completely relieved of symp toms and showed near total or total resolution of the CSDH on CT after 6–8 weeks. Two patients developed steroidrelated complications. Gender, midline shift, thickness of haematoma and Hounsfield units of the haematoma on CT showed statistically significant differences when the failure group was compared with the success group. The authors then proposed a radiological grading scale that can help predict the chance of successful treatment with corticosteroids. They conclude that in

patients with low grades (0–2) corticosteroid treatment might be more successful than in high grades (4 and 5).[64]

A pilot randomised controlled trial recently initiated in Canada enrolled 10 patients treated with steroids (dexamethasone 4 mg three times a day for 3 weeks with tapering for a week) and 10 patients who received placebo. The study was terminated after 20 patients had been recruited because 80% of the patients receiving steroids suffered a serious adverse event as opposed to 10% of the patients in the placebo group.[65]

Angiotensin converting enzyme inhibitors

The effect of ACE inhibitors on the course of CSDH remains unclear. ACE inhibitors are used for the treatment of arterial hypertension, but also for pathologies with increased angiogenic activity such as Kaposi's syndrome and diabetic retinopathy.[66] On the basis of the angiogenic hypothesis of CSDH, it is assumed that ACE inhibitors might lower the risk for developing a CSDH and for its recurrence.[66] However, contrary data have been presented, since ACE inhibitors are known to increase the levels of bradykinin, the end product of the kallikrein-kinin system. Bradykinin, a vasoactive peptide, induces both permeability and vasodilatation, and leads to blood extravasation from the neomembranes in CSDH, leading to an enlargement of the haematoma.[67] Studies evaluating ACE inhibitors as a conservative medical treatment for CSDH do not exist. However, three studies evaluated the effect of ACE inhibitors during the postsurgi cal course of CSDH. Weigel et al.[66] showed a lower recurrence rate of CSDH after surgical drainage in patients treated with ACE inhibitors for hypertension. They concluded that ACE inhibitors lower recurrence rate and might even lower the risk of developing a CSDH (type C recommendation). In a randomised controlled study in which an ACE inhibitor (perindopril) was given for 3 months postoperatively and compared with placebo, no significant difference in recurrence rates was seen.[68] The authors concluded that ACE inhibitors do not lower recurrence rates after surgical drainage of CSDH (type B recommendation). Unfortunately, other studies evaluating the effect of ACE inhibitors as adjuvant treatment with the surgical evacuation of CSDH and as stand-alone conservative treatment do not exist. Based on the available data, the benefit of ACE inhibitors as an adjuvant treatment to the surgical evacuation of CSDH is ambiguous. ACE inhibitors do not seem to reduce the

recurrence rate of CSDH and cannot be recommended at this point (type B recommendation). Studies examining the efficacy of ACE inhibitors as a stand-alone conservative treatment do not exist and therefore no recommendation can be made (table 4). Further studies evaluating the benefit of ACE inhibitors as a conservative treatment option for CSDH are warranted.[56] Tranexamic acid Fibrinolytic and coagulative hyperactivity seem to play a role in the liquefaction and progression of CSDH.[69] In addition, increased permeability of the capillaries in the outer haematoma membrane lead to microbleeds that influence haematoma growth.[56] The kallikrein system, which is activated by plasmin, induces inflammation and therefore increases vascular permeability and leucocyte migration, and was found to be present in the outer membrane of CSDH.[69] Tranexamic acid has an antifibrinolytic effect via inhibition of plasminogen activator and plasmin. Therefore, it is hypothesised that tranexamic acid might inhibit the hyperfibrinolytic activity and the increased vascular permeability in CSDH, leading to a gradual absorption of the haematoma.[69] Based on these assumptions, a retrospective study analysing the influence of tranexamic acid on CSDH managed conservatively was conducted by Kageyama et al.[69] They showed, in 18 patients treated with 750 mg of tranexamic acid once a day, a complete resorption of all haematomas and therefore concluded that tranexamic acid might be a valid conservative treatment for CSDH (type C recommendation). Adverse events associated with tranexamic acid were not seen in their cohort. However, patients with anticoagulation were excluded from the study, and therefore the effect of tranexamic acid on anticoagulated patients remains unknown; in these patients tranexamic acid should be applied with caution. To date the role of tranexamic acid in the treatment of CSDH is still uncertain; in particular, its effect on the resorption of CSDH and the adverse event rate, especially in patients at risk for thromboembolic events, is still to be evaluated in larger studies and therefore recommendations cannot be made. A placebo-controlled phase IIB randomised controlled (TRACS) aiming to determine whether tranexamic acid can increase the rate of resolution and lower the need for surgical evacuation of CSDH when treated conservatively is currently ongoing.[70] Mannitol Mannitol is an osmotic diuretic used for the treatment of increased intracranial pressure.[71] In cSDH it was hypothesised that the haematoma increases as a result of an osmotic gradient within the haematoma capsule. Consequently, increase of haematoma produces strain to the capsule, leading to microbleeds and further enlargement of the haematoma. Reduction of haematoma pressure using mannitol

might prevent this chain of events, stopping the continuous rebleeding inside the haematoma cavity and ultimately allowing spontaneous resorption of the haematoma.[71] Based on these assumptions, Suzuki et al. administered a 500–1000 ml mannitol drip (20%) daily as a conservative treatment modality for CSDH.[71] Of 23 consecutive patients, 22 showed decreasing haematoma volume and complete neurological recovery at follow up, whereas in one case burr hole drainage was needed after 12 days of mannitol treatment. The duration of mannitol treatment ranged from 12 to 106 days, which is definitely a drawback of this treatment. The authors concluded that mannitol can be used for the conservative treatment of CSDH. They recommend using a dose of 1000 ml, since it showed better results than a dose of 500 ml, and if the treatment does reduce symptoms after 3 to 4 days, surgical evacuation should be undertaken immediately (type C recommendation). In another study from Japan, 20 patients treated with mannitol (20%) 1000 ml daily intravenously for 2 weeks were screened. During the first and second week of treatment, four patients showed aggravated symptoms. However, at the end of follow-up all, cases were asymptomatic and after 5 months there was complete resolution of all haematomas on CT.[72] These results suggest that mannitol may have a role in the conservative treatment of CSDH.

Published studies on corticotherapy for CSH

Authors	N	Outcome & Comments
Ambrosetto C (1962)1	3	The three patients resolved within few months (improved within 2-4 weeks) with a combination of bed rest, vitamin supplement, corticoids (not specified), intravenous injection of hypertonic glucose solutions and other drugs. Diagnosis and follow up done with cerebral angiogram.
Bender MB & Christoff N (1974)2	27	All improved after 24 hours. Used prednisone 60mg for 21 days average. Diagnosis and follow up done with cerebral angiogram. Ten patients (37%) needed surgery afterwards due to clinical stabilization or deterioration after 72 hours.
Victoratos GC & Bligh AS (1981)29	1	Dexamethasone (dose not reported) for one week. Headache resolved in 48 hours. CT based image follow up.
Parajuá M et al (1984)22	3	Dexamethasone (16 mg per day intramuscular). Clinical improvement (immediately after initiation of steroids) preceded radiological resolution (6,6 and 4 months after corticotherapy). Full recovery of all three cases.
Inzelberg R et al (1989)13	1	Intravenous dexamethasone (dose not reported). Complete resolution of hemiparesis and dysphasia. Patient on anticoagulant medication for haemodialysis. CT based image follow up.
Rudiger A et al (2001)23	1	Dexamethasone 4mg/12 hours. Seventy-six year-old diabetic patient presenting with confusion and ataxia, harbouring a bilateral CSH. Surgery impossible because of anaesthetic problems. Developed hyperglycaemic impairment that needed insulin therapy. Resolved completely in a few days. CT image normal alter 6 weeks.
Decaux O et al (2002)3	02	Cortancyl® (cortisone 1mg/Kg/day). Complete early clinical and radiological resolution.
Sun TFD et al (2005)26	26	Dexamethasone 4mg/6h for 21 days. Patients in old age with medical co-morbidity or who refused surgical treatment. Twenty-three patients (84%) achieved favourable outcome. Surgical drain plus steroids reduced the chance of re-accumulation.
Present series	101	Dexamethasone 4mg/8h, re-evaluation after 48-72h and corticoids tapered down. Favourable results in 71/73 exclusively managed with dexamethasone. Needed surgical drainage 22 patients out of 101.

METHODOLOGY

Type of study

Prospective open labeled randomized controlled clinical trial.

Place of study

Dhaka Medical College Hospital.

Department: Emergency,Neurosurgery & Neurology.

Duration of study

From 10.06.2012 to 09.06.2016.

Study population

Patients visited at emergency & admitted in the neurology & Neurosurgery department of DMCH having non contrast enhanced CT scan suggestion of CSDH.

Inclusion criteria

Age:>18 yrs or older

Sex:Male or Female

CSDHs diagnosed:

Clinically and

Radiologically.

Clinically

Headache

Altered mental status.

Vomiting

Contra lateral limb weakness

Speech disorder

Vertigo

Seizure

Radiologically

Non-contrast CT scan of head showing chronic subdural haematoma.

CT Findings

There should be a hypodense / isodense / mixed dense area located just under the dura (Non-contrast film) with evidence of midline shifting<10 mm.

MGS grade#1-3

(MGS#The validated grading system score 0-4 for the severity of neurological symptoms).

Exclusion criteria

Patient with use of antithrombolytic and anticoagulant drugs.

Age less than 18 years.

CT scan showing signs of midline shifting>10mm,Uncal transtentorial herniation, acute haemorrhage or loculations or membrane formation within CSDH.

Skull fracture over the subdural haematoma.

Presence of PUD,Psychosis,active TB,acute infection & documented hypersensitivity to DXM.

Sample size and statistical basis

Sample size depends on effect size, variance, Alpha+beta error, power and precession. Prevalence of chronic subdural haematoma is not known in our country. So estimated population was calculated by using the following statistical formula:

$$n = \frac{P_1 (1- P_1) + P_2 (1- P_2)}{(P_1-P_2)^2} \times (Z_\alpha+Z_\beta)^2$$

Here $P_1 = 0.50$

$P_2 = ?$

$Z_\alpha = 1.96$ (at 5% level of significance)

$Z_\beta = 0.85$ (at 80% power)

n = 95 (sample size for each group).

During the screening phase after verification of selection criteria 103 participants(Patients) were selected but have lost 43 patients during BHC & DXM medication.Due to unavailability of patients, finally 60 patients were included according to selection criteria. They were equally divided into Steroid group and Surgery group. They were diagnosed as CSDH by non-contrast CT scan of head. The patients were selected meeting the specific criteria.

Sampling technique

Purposive sampling (randomized) according to availability of the patients and strictly considering the inclusion and exclusion criteria.

Variables

A. Demographic and clinical variables

Age of the patient

sex of the patient

Glasgow comma scale at the presentation.

B. Imaging variables (CT scan related variables)

Side and site of the haematoma

Shifting of the midline

Medical management variables

Steroid given or not.

Medical outcome variables

Glasgow coma scale (GCS)

Glasgow outcome scale (GOS)

The Markwalder scale of CSDH

mRS(Modified Rankin Scale)

QOL(SF-36)

QOL/BRI overall scale.

Data collection procedure

Data was collected with a pre-tested structured questionnaire containing history, clinical examination and laboratory investigations.

On admission, a detailed history of the illness was taken from the patients / patients' attendant.

General and neurological examinations were performed next.

GCS score and Markwalder scale were determined and recorded.

Findings of CT scan were recorded.

Operative findings were noted and recorded in the data sheet.

Data collection

After enrollment of the patient, the data of the selected variables (mentioned earlier) was collected.

Data processing and data analysis

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

The mean values were calculated for continuous variables.

The quantitative observations were indicated by frequencies and percentages.

Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. P values <0.05 was considered as statistically significant.

Ethical consideration

Informed written consent was taken from the patient or patient's guardian after duly informing the procedure of treatment, anticipated result, possible advantages, disadvantages and complications considering all ethical issues.

Confidentiality was maintained both verbally and documentary by using separate locker and computer password.

Protocol was approved by ethical committee of Dhaka Medical College Hospital (Ref. DMC/Ethical/2013/140, dated 21.07.2013).

OBSERVATION AND RESULTS

Table 5: Distribution of the study patients by age (n=60)

Age (years)	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
21-40	6	20.0	3	10.0	
41-60	7	23.3	12	40.0	
61-80	10	33.3	14	46.7	
>80	7	23.3	1	3.3	
Mean±SD	64.1±19.8		61.5±12.2		0.548^{ns}
Range (min-max)	26-90		40-90		

ns= not significant

P value reached from chi square test

Table shows age distribution of the study patients, it was observed that one third (33.3%) patients were belonged to age 61-80 years in steroid group and 14(46.7%) in surgery group. The mean age was found 64.1±19.8 years in steroid group and 61.5±12.2 years in surgery group. The mean age was not statistically significant ($p>0.05$) between two groups.

Table 6: Distribution of the study patients according to sex (n=60)

Sex	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Male	26	86.7	25	83.3	0.500[ns]
Female	4	13.3	5	16.7	

ns= not significant

P value reached from chi square test

Table shows sex of the study patients, it was observed that majority (86.7%) patients were male in steroid group and 25(83.3%) in surgery group. The difference was not statistically significant (p>0.05) between two groups.

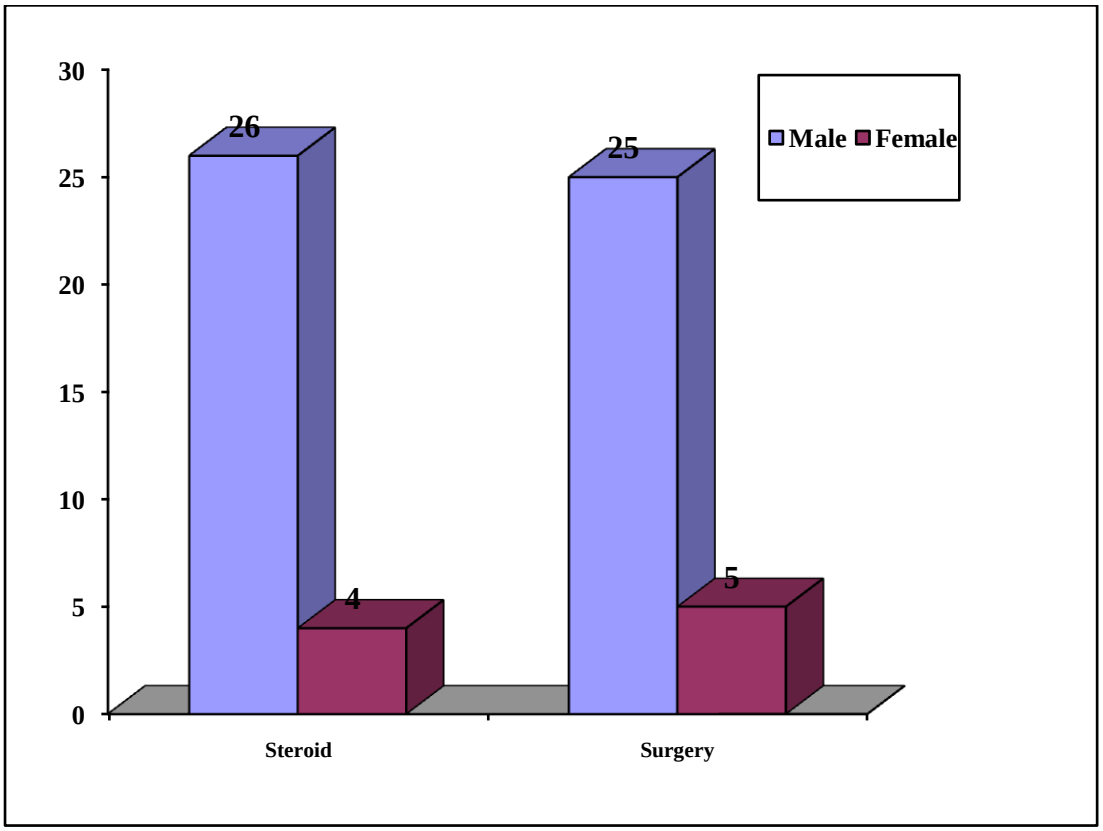


Figure 25: Bar diagram showing sex distribution of the patients

Table 7: Distribution of the study patients the Glasgow coma scale before treatment (n=60)

Before treatment Glasgow coma scale (GCS)	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
9-12	6	20.0	9	30.0	0.371[ns]
13-15	24	80.0	21	70.0	

ns= not significant

P value reached from chi square test

Table shows before treatment Glasgow coma scale of the study patients, it was observed that majority (80.0%) patients was found before treatment Glasgow coma 13-15 scale in steroid group and 21(70.0%) in surgery group. The difference was not statistically significant (p>0.05) between two groups.

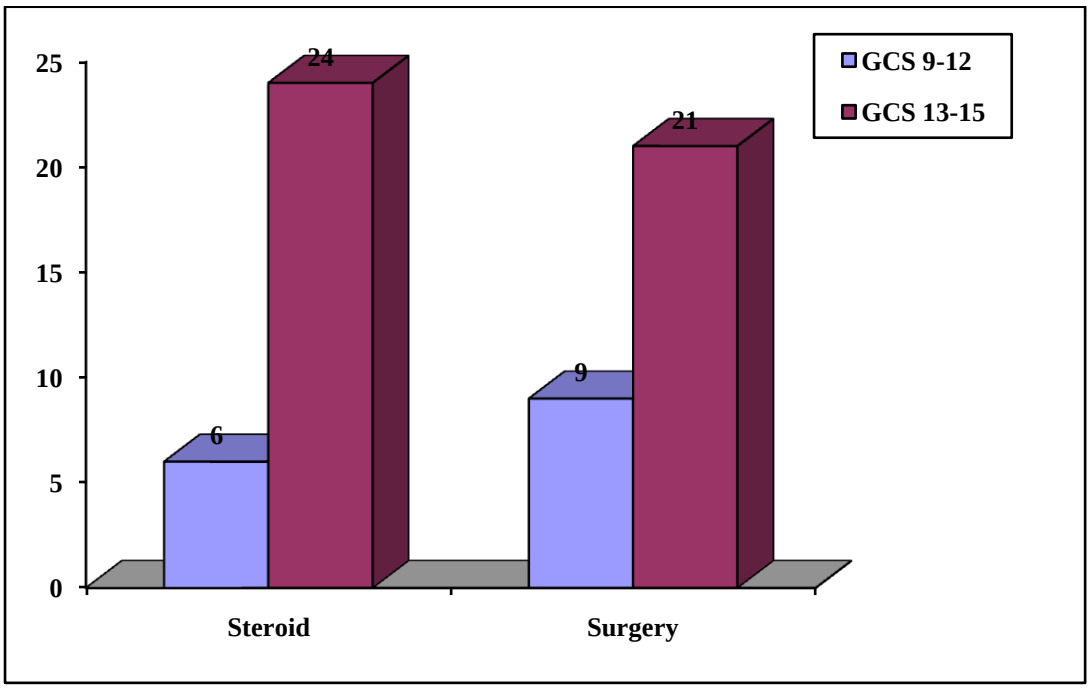


Figure 26: Bar diagram showing before treatment Glasgow coma scale of the patients

Table 8: Distribution of the study patients according to motor weakness (n=60)

Motor weakness	Steroid (n=30)		Surgery (n=30)		p value
	n	%	n	%	
Absent	22	73.3	10	33.3	0.001[s]
Present	8	26.7	20	66.7	
Hemiplegia	8	26.7	18	60.0	
Monoplegia	0	0.0	2	6.7	

s= significant

P value reached from chi square test

Table shows motor weakness of the study patients, it was observed that more than one fourth (26.7%) patients had motor weakness in steroid group and 20(66.7%) in surgery group. The difference was statistically significant ($p<0.05$) between two groups.

Table 9: Distribution of the study patients according to truma (n=60)

Truma	Steroid (n=30)		Surgery (n=30)		p value
	n	%	n	%	
Present	15	50.0	18	60.0	0.436[ns]
Absent	15	50.0	12	40.0	

ns= not significant

P value reached from chi square test

Table shows truma of the study patients, it was observed that half (50.0%) patients had truma in steroid group and 18(60.0%) in surgery group. The difference was not statistically significant (p>0.05) between two groups.

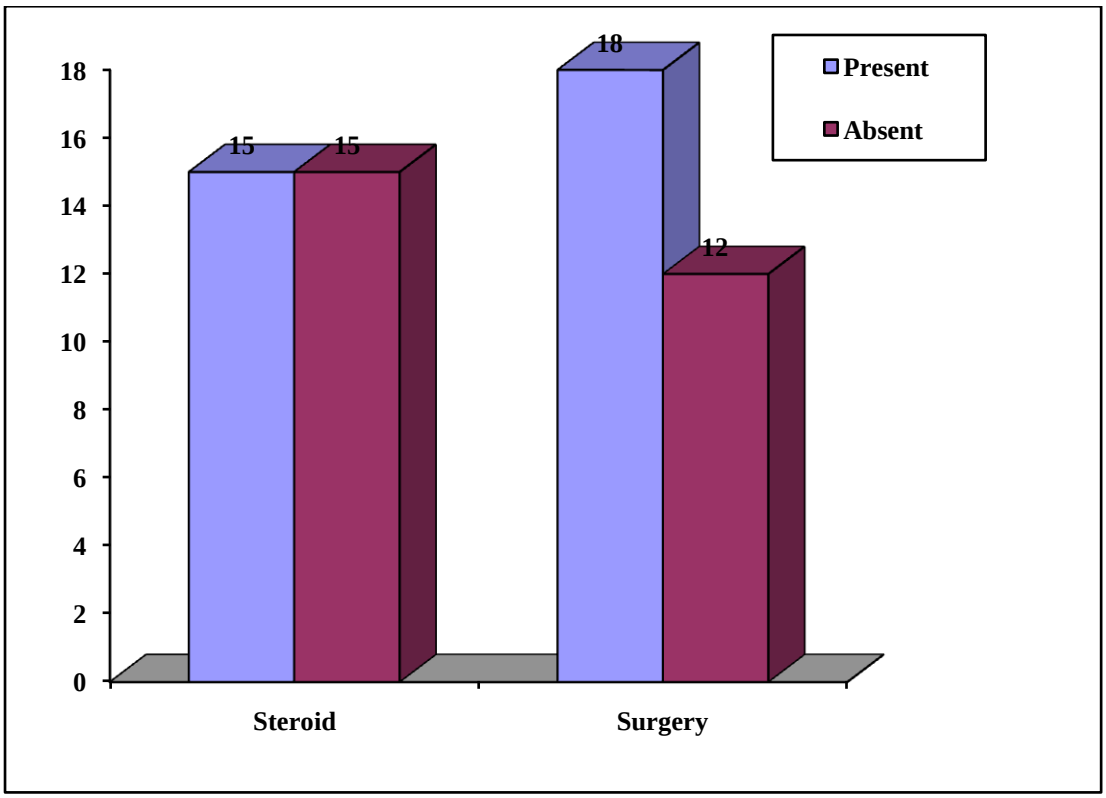


Figure 27: Bar diagram showing truma of the patients

Table 10: Distribution of the study patients according to side (n=60)

Side	Steroid (n=30)		Surgery (n=30)		p value
	n	%	n	%	
Right	12	40.0	9	30.0	
Left	14	46.7	13	43.3	0.407[ns]
Bilateral	4	13.3	8	26.7	

ns= not significant

P value reached from chi square test

Table shows side of the study patients, it was observed that almost half (46.7%) patients was found left side haematoma in steroid group and 13(43.3%) in surgery group. The difference was not statistically significant (p>0.05) between two groups.

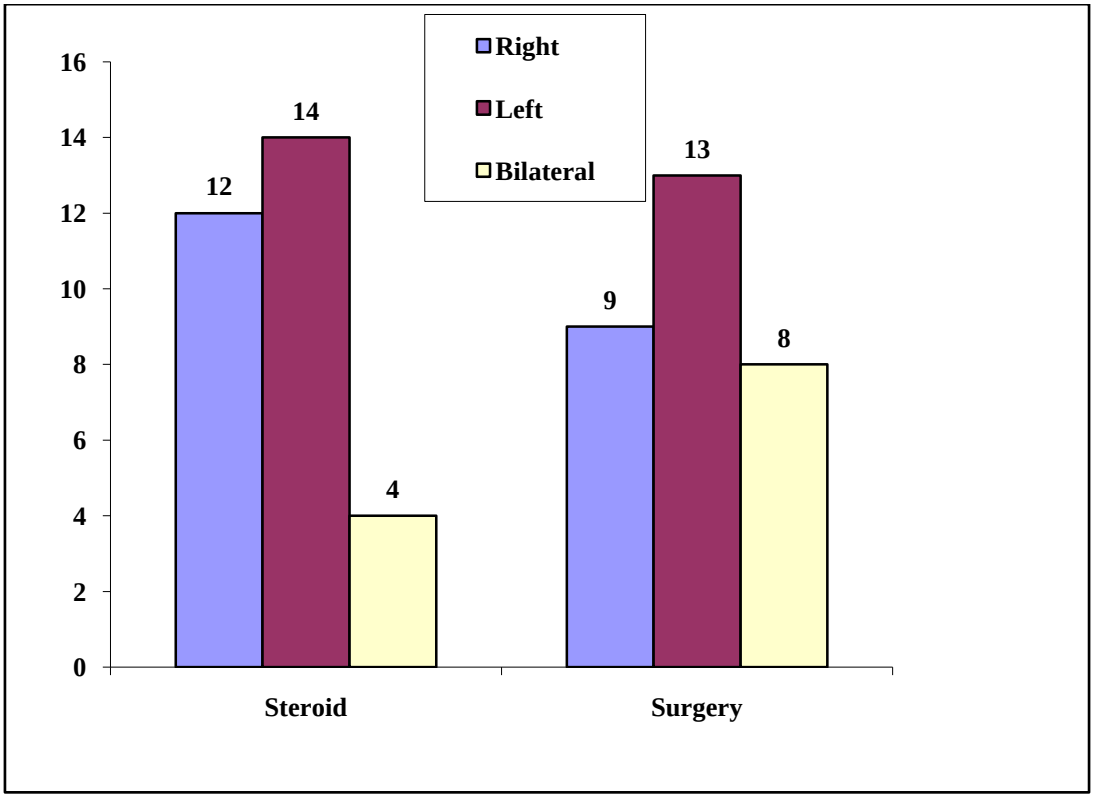


Figure 28: Bar diagram showing side of the patients

Table 11: Distribution of the study patients according to psychic function (n=60)

Psychic function	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Normal	25	83.3	18	60.0	0.045[s]
Disoriented	5	16.7	12	40.0	

s= significant

P value reached from chi square test

Table shows psychic function of the study patients, it was observed that majority (83.3%) patients were psychic function normal in steroid group and 18(60.0%) in surgery group. The difference was statistically significant ($p<0.05$) between two groups.

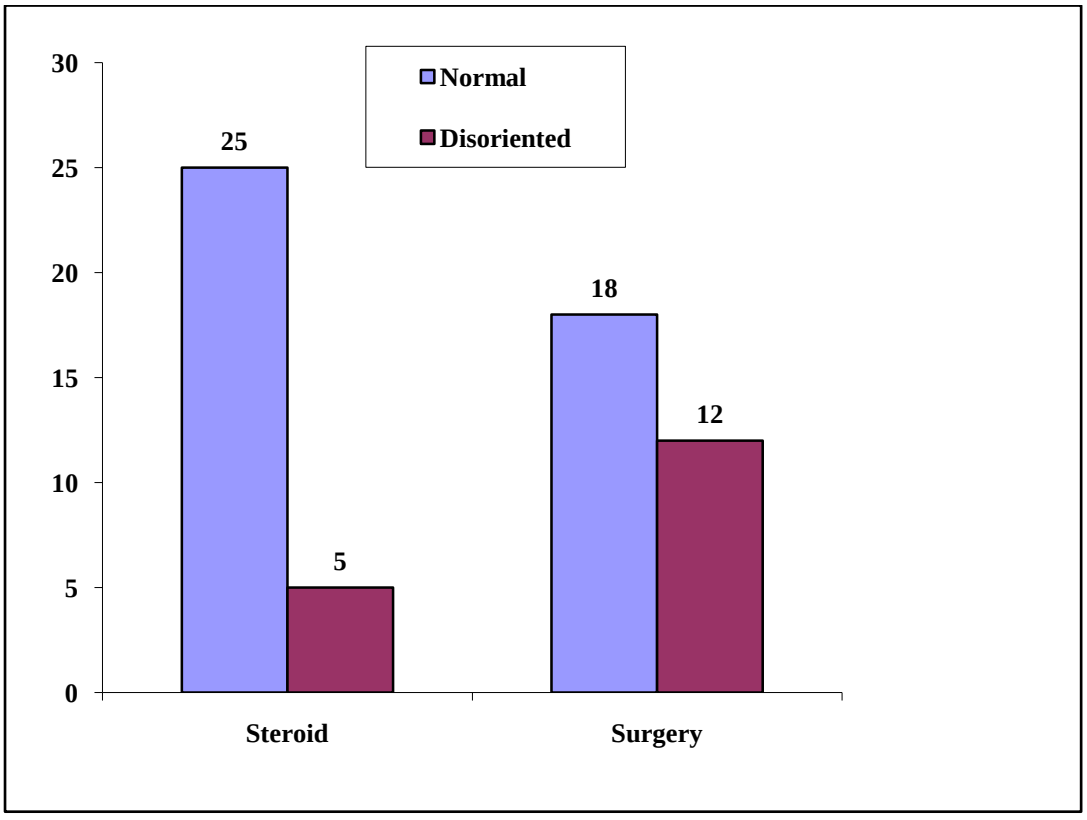


Figure 29: Bar diagram showing psychic function of the patients

Table 12: Distribution of the study patients according to headache (n=60)

Headache	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
No	18	60.0	12	40.0	
Mild	10	33.3	9	30.0	0.110^{ns}
Moderate	2	6.7	7	23.3	
Severe	0	0.0	2	6.7	

ns= not significant

P value reached from chi square test

Table shows headache of the study patients, it was observed that 10(33.3%) patients had mild headache in steroid group and 9(30.0%) in surgery group. The difference was not statistically significant (p>0.05) between two groups.

Table 13: Distribution of the study patients according to vomiting (n=60)

Vomiting	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Present	11	36.7	16	53.3	0.194^{ns}
Absent	19	63.3	14	46.7	

ns= not significant

P value reached from chi square test

Table IX shows vomiting of the study patients, it was observed that more than one third (36.7%) patients had vomiting in steroid group and 16(53.3%) in surgery group. The difference was not statistically significant (p>0.05) between two groups.

Table 14: Distribution of the study patients according to site (n=60)

Site	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Parietal	25	83.3	12	40.0	0.001[s]
Left fronto pariental	5	16.7	18	60.0	

s= significant

P value reached from chi square test

Majority (83.3%) patients had parietal site in steroid group and 12(40.0%) in surgery group. The difference was statistically significant ($p<0.05$) between two groups.

Table 15: Distribution of the study patients according to size (n=60)

Size	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Small	4	13.3	6	20.0	
Medium	6	20.0	7	23.3	0.698[ns]
Large	20	66.7	17	56.7	

ns= not significant

P value reached from chi square test

Table shows size of the study patients, it was observed that two third (66.7%) patients was found large size in steroid group and 17(56.7%) in surgery group. The difference was not statistically significant ($p>0.05$) between two groups.

Table 16: Distribution of the study patients the markwalder CSDH grading scale after treatment (n=60)

After treatment Markwalder CSDH grading scale (MGS)	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Grade I	24	80.0	21	70.0	
Grade II	5	16.7	8	26.7	0.640[ns]
Grade III	1	6.7	1	6.7	

ns= not significant

P value reached from chi square test

Table shows after treatment markwalder CSDH grading scale of the study patients, it was observed that majority (80.0%) patients was found grade I markwalder CSDH after treatment in steroid group and 21(70.0%) in surgery group. The difference was not statistically significant (p>0.05) between two groups.

Table 17: Distribution of the study patients the Glasgow outcome scale after treatment (n=60)

After treatment Glasgow Outcome Scale (GOS)	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
GOS 5 (good recovery)	24	80.0	16	53.3	0.028[s]
GOS 4 (moderate disability)	1	3.3	1	3.3	0.754[ns]
GOS 3 (severe disability)	2	6.7	7	23.3	0.073[ns]
GOS 2 (vegetative state)	1	3.3	4	13.3	0.177[ns]
GOS 1 (Death)	2	6.7	2	6.7	0.694[ns]

s= significant, ns= not significant

P value reached from chi square test

Table shows after treatment Glasgow outcome scale of the study patients, it was observed that majority (80.0%) patients was found GOS 5 (good recovery) after treatment in steroid group and 16(53.3%) in surgery group. The difference was statistically significant ($p<0.05$) between two groups.

Table 18: Distribution of the study patients according to outcome (n=60)

Outcome	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Normal	25	83.3	17	56.7	
Recurrence	3	10.0	11	36.7	0.047[s]
Death	2	6.7	2	6.7	

s= significant

P value reached from chi square test

Table shows outcome of the study patients, it was observed that majority (83.3%) patients was found normal in steroid group and 17(56.7%) in surgery group. The difference was statistically significant ($p<0.05$) between two groups.

Table 19: Distribution of the study patients according to CT finding (n=60)

CT finding	Steroid (n=30)		Surgery (n=30)		P value
	n	%	n	%	
Hypodense	10	33.3	11	36.7	
Isodense	9	30.0	6	20.0	0.665[ns]
Mixed density	11	36.7	13	43.3	

ns= not significant

P value reached from chi square test

More than one third (36.7%) patients were mixed density on CT findings in steroid group and 13(43.3%) in surgery group. The difference was not statistically significant ($p>0.05$) between two groups.

DISCUSSION

The randomized controlled clinical trial was carried out in the Neurology and Neurosurgery Department of Dhaka Medical College Hospital. All Patients admitted in the neurology & Neurosurgery development of DMCH having non contrast enhanced CT scan suggestion of CSDH. A total of 60 Patients, meeting the specific criteria and was admitted during the study period in the neurology & neurosurgery department of DMCH were included in this study. They were equally divided into two groups. They were diagnosed as CSDH by non-contrast CT scan of head. The patients were selected meeting the specific criteria.

In this present study it was observed that one third (33.3%) patients were belonged to age 61-80 years in steroid group and 14(46.7%) in surgery group. The mean age was found 64.1±19.8 years in steroid group and 61.5±12.2 years in surgery group. The mean age was not statistically significant ($p>0.05$) between two groups. Chan et al.[73] the mean age was found 70.8 years in surgery group and 71.9 years in steroid+ surgery group. Santarius et al.[74] showed the mean age of the participants was 76.8 years (SD=10.6), ranging from 36 years to 95 years. Mori and Maeda[6] study the mean age was 67.3±15.3 years for the male patients and significantly higher ($p<0.01$) at 71.3±14.2 years for the female patients. Wang et al.[75] study observed the mean age of patients was 80.9 ± 7.1 years in the surgical group and 82.5 ± 6.9 years in the conservative group.

In this current study it was observed that majority (86.7%) patients were male in steroid group and 25(83.3%) in surgery group. The difference was not statistically significant ($p>0.05$) between two groups. Chan et al.[73] observed that 38 (30.2%) patients were female in surgery group and 33(27.0%) in steroid+ surgery group. The difference was not statistically significant ($p>0.05$) between two groups.

In this study it was observed that majority (80.0%) patients was found before treatment Glasgow coma 13-15 scale in steroid group and 21(70.0%) in surgery group. The difference was not statistically significant ($p>0.05$) between two groups. Das et al.[76] was revealed that 140 patients was found GCS 14-15 scale in pre-operative and 13 cases in post-operative.

In this present study it was observed that half (50.0%) patients had turmatic in steroid group and 18(60.0%) in surgery group. The difference was not statistically significant

(p>0.05) between two groups. Wang et al.[75] CSDH is a condition mostly present in elder people, and the majority of patients had a history of head trauma, as noted in our series and in the literature. Senturk et al.[77] showed out of the 34 patients 19 (56%) had a history of head trauma, which in all cases, except for two motor vehicle accidents, was minor.

In this study it was observed that almost half (46.7%) patients was found left side haematoma in steroid group and 13(43.3%) in surgery group. The difference was not statistically significant (p>0.05) between two groups. Chan et al.[73] was showed 52(41.3%) patients were left side in surgery group and 58(47.5%) in steroid+ surgery group. The difference was not statistically significant (p>0.05) between two groups.

In this series it was observed that 10(33.3%) patients had mild headache in steroid group and 9(30.0%) in surgery group. The difference was not statistically significant (p>0.05) between two groups. Wang et al.[75] showed 12 (38.7%) patients had headache in the surgical group and 7(31.8%) in the conservative group. The difference was not statistically significant (p>0.05) between two groups.

In this study it was observed that majority (80.0%) patients was found grade I markwalder CSDH after treatment in steroid group and 21(70.0%) in surgery group. The difference was not statistically significant (p>0.05) between two groups. Chan et al. 2015 Eighty nine (70.6%) patients was found MGS grade I in surgery group and 99(81.1%) in steroid+ surgery group. The difference was not statistically significant (p>0.05) between two groups. Emich et al.[78] out of 122 patients were enrolled and divided into two groups: Subjects with a good neurological condition (Markwalder grading score (MGS) 0 to 2) were assigned to the dexamethasone protocol, whereas patients with MGS 3 to 4 were assigned to a surgical protocol. Of the 122 patients, 101 were on dexamethasone, and 22 of them ultimately required a surgical drain (21.8%). A favorable outcome (MGS 0, 1, or 2) was obtained in 96% and 93.9% of those treated with dexamethasone and surgical drain, respectively.

In this series it was observed that majority (80.0%) patients was found GOS 5 (good recovery) after treatment in steroid group and 16(53.3%) in surgery group. The difference was statistically significant (p<0.05) between two groups. Chan et al.[73] showed that 91(72.2%) patients was found GOS 5 in surgery group and 99(81.1%) in

steroid+ surgery group. The difference was not statistically significant (p>0.05) between two groups. Das et al.[76] most patients with CSDH (89%) recovers after burr hole craniostomy with closed system drainage. 15% suffer recurrence of haematoma and developed complications, death 2%. In this study good recovery was 94%, complication was 4%, and death 2% which co-relates with international study.

In this present study it was observed that majority (83.3%) patients was found normal in steroid group and 17(56.7%) in surgery group. The difference was statistically significant (p<0.05) between two groups. Chan et al.[73] three (2.38%) patients was found death in surgery group and 3(2.46%) in steroid+ surgery group. The difference was not statistically significant (p>0.05) between two groups. Delgado-Lopez et al.[1] described 101 patients who were primarily treated with corticosteroids alone, of which 71 (70.3%) had good neurological outcome, needing no further treatment and improvement appearing soon after initial dose. Fourteen of 19 (73.7%) patients had good neurological outcome in the surgical group. Improvements after initial corticosteroid dose were reported. Two of 26 patients (8%) in the prospective study were severely disabled, four of 69 patients (6%) in the combination group, compared with 8% in the surgically treated patients.

In this current study it was observed that more than one third (36.7%) patients were mixed density on CT findings in steroid group and 13(43.3%) in surgery group. The difference was not statistically significant (p>0.05) between two groups. Senturk et al.[77] eighteen haematomas (38%) were hypodense and 10 (21%) were isodense on CT scans. In addition, 19 (40%) haematomas were mixed density and only 1 (2%) was hyperdense. Computed tomography remains the most important imaging method in the initial evaluation of CSDHs. MR imaging is more advantageous in the case of isodense and bilateral CSDHs. CT and MR imaging of CSDHs detect various patterns, which can be attributed to many factors including the age of the haematoma, the presence of rehaemorrhage and the haematocrit status of the patient. Das et al.[76] showed CT demonstrated CSDH as hypodense (45%), isodense (40%), and hyperdense (15%) in relation to Cerebral Parenchyma haematoma thickness varies from 15-25 mm unilaterally and 20-39 bilaterally.

SUMMARY

The study was a Randomized controlled clinical trial study was carried out at the Department of Neurology and Neurosurgery of Dhaka Medical College Hospital. A total of 60 Patients, meeting the specific criteria and was admitted during the study period in the neurology & neurosurgery department of DMCH was included in this study. They were equally divided into two groups. They were diagnosed as CSDH by non-contrast CT scan of head. The patients were selected meeting the specific criteria. The mean age was found 64.1±19.8 years in steroid group and 61.5±12.2 years in surgery group. Majority (86.7%) patients were male in steroid group and 25(83.3%) in surgery group. Majority (80.0%) patients was found before treatment Glasgow coma 13-15 scale in steroid group and 21(70.0%) in surgery group. More than one fourth (26.7%) patients had motor weakness in steroid group and 20(66.7%) in surgery group. Half (50.0%) patients had turmatic in steroid group and 18(60.0%) in surgery group. Almost half (46.7%) patients was found left side haematoma in steroid group and 13(43.3%) in surgery group. Majority (83.3%) patients were psychic function normal in steroid group and 18(60.0%) in surgery group. The difference was statistically significant ($p<0.05$) between two groups. Ten (33.3%) patients had mild headache in steroid group and 9(30.0%) in surgery group. More than one third (36.7%) patients had vomiting in steroid group and 16(53.3%) in surgery group. Majority (83.3%) patients had parietal site in steroid group and 12(40.0%) in surgery group. Two third (66.7%) patients was found large size in steroid group and 17(56.7%) in surgery group. Majority (80.0%) patients was found grade I markwalder CSDH after treatment in steroid group and 21(70.0%) in surgery group. majority (80.0%) patients was found GOS 5 (good recovery) after treatment in steroid group and 16(53.3%) in surgery group. The difference was statistically significant ($p<0.05$) between two groups. Majority (83.3%) patients was found normal in steroid group and 17(56.7%) in surgery group. More than one third (36.7%) patients were mixed density on CT findings in steroid group and 13(43.3%) in surgery group.

Conclusion

This noble therapeutic approach to CSDH opposes the traditional view of neurosurgeons that are prone to indicate early surgery. We do not advocate for the substitution of surgery by steroid medication but to consider glucocorticoids a conservative alternative in the majority of cases. Within the limitations of this prospective analysis, the effectiveness, safety and applicability of steroids seem comparable to those of surgery and eliminate all possible morbidities of interventions. Of course, the true role of glucocorticoids in the management of CSDH as compared to surgical techniques should be ideally subject of analysis in a multi-centre, prospective, randomized and controlled trial. The preliminary information offered by our prospective case review may be a starting point for future studies in assessing the real effectiveness and safety of corticotherapy in this disease. The morbidity,mortality is high in surgical drainage. DXM therapy in treating CSDH is safe,beneficial & showing promising results as an alternative to Craniostomy & surgical drainage. It inhibits the formation of new blood vessels by its anti-inflammatory & antiangiogenic effects. Non-invasive, reduce mortality & better outcome. Led to shorter hospitalization. More costeffective compared with BHC & avoid reoperation.

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Appendices

Appendix-1

DATA RECORDING SHEET

Department of Neurosurgery / Neurology

Dhaka Medical College Hospital, Dhaka.

Sl. No: Date :

PARTICULARS OF THE PATIENT

Name :	Reg. No:
Sex :	Ward :
Age :	Unit :
Address :	Bed :
Phone :	
Date of Admission :	Time :
Date of Operation :	Time :
Date of discharge :	Time :

HISTORY SHEET

Clinical Presentation :

1. Neurological deficit:			
Cranial nerve palsy :	Involved nerve	Site	Absent
Motor symptoms :			
Sensory symptoms :			
Autonomic :			

2. H/O:		
	1=Duration	2 = Absent
Headache		
Visual disorder		
Vomiing		
Speech disorder		
Tremor		
Behavioral disorders		
Speech disorder		
Motor disorder		
Sensory disorder		
Sphincter disorder		
Lower cranial nerve disorder		
Mental disorder		
Loss of consciousness		
Convulsion		
Tuberculosis		
Maligancy		
Hypertension		
Diabetes mellitus		

EXAMINATION FINDINGS

General Examination	
Pulse	
Blood Pressure	
Respiration	

2. Neurological examination		
GCS (Glasgow coma scale)	[EVM}	
Higher Psychic function :		
Cranial Nerves		
Pupils	Size	
	Reaction	
Motor system		
	Appearance	
	Tone	
	Power	
	Bulk	
	Jerks	
Sensory System		
Co-ordination		
Autonomic function		

Pre-morbid

Mobility

Independent

Stick

Zimmer frame

Wheelchair

Bed-bound

Residence

Independent

Carer

Residential

Nursing

Medical history

Dementia

Arrhythmia

Cerebrovascular accident

Hypertension

Ischaemic heart disease

DVT or PE

COPD

Diabetes

Drug history

Anticoagulant*

Antiplatelet*

Admission

Glasgow coma scale

13 – 15

9 – 12

3 – 8

MRS score

0

1

2

3

4

5

MRS score (median)

Hemiparesis

Dysphasia

CT

Hypodense

Isodense

Mixed

Midicine shift (mm)

Side

Left

Right

Bilateral

Investigations related to the procedure

1. CT scan of brain	
ID No :	
Data & Time of doing CT	
Scan :	
Findings :	
Site	
Size	
Number	
Shape	
Pre-lesional oedema	
Density	Hyper
	Hepo
	Mixed
	Positive
	Negative
	Interpretation

2. MRI FINDINGS (If available)

ID No :			
Findings :			
Site :			
Size :			
Number			
Shape			
Peri-iesional oedema			
Intensity	T_1	T_2	Flair
Hyper			
Hypo			
Mixed			

Contrast uptake	Positive	
	Negative	
	Interpretation	
3. BT		
4. CT		
5. Prothrombin Time	Patient	
	Control	
	INR	
6. APTT		
7. Other related investigations		
RBS		
Blood urea		
Serum creatinine		
Serum electrolytes	No'	k'
	Cl	HC_3

PRE OPERATIVE ASSESMENT OF LEISON AFTER PLACEMENT OF HEADFRAME (AS PER MANUAL)

X-X' –(X VALVE)	
Y-Y' –(Y VALVE)	
Z-Z' –(Z VALVE)	

CONTRAST UPTAKE DURING PROCEDURE (IF NEEDED)
OPERATION

1. Date & Time of operation :	
Position	
Incision	Site

FOLLOW UP				
Psychic function	Normal	Disoriented	Unconscious	
GCS (EVM)				
Headache	No	Mild	Moderate	Severe
Vomiting	Present		Absent	
Speech	Normal	Dysphasia	Aphasia	
Motor weakness (if any)	Absent	Hemiptegia	Monoplegia	
New swelling at biopsy site	Present		Absent	
Post operative ct scan (if performed)				

Grade 4 4 3 2 1 0

Rt. Upper Limb

Lt. Upper Limb

Rt. Lower Limb

Lt. Lower Limb

Investigation Performed

CT Scan

MRI

Others

Date of Operation

Operative Findings

Complications

Associated Medical conditions : DM, HTN, Epilepsy, STI,

Determination of outcome by GCS at discharge

Follow-up period in 2 months :

Clinical : GCS KPS

Radiological : MRI

Follow-up period in 4 months :

Clinical : GCS KPS

Radiological : MRI

Follow-up period in 6 months :

Clinical : GCS KPS

Radiological : MRI

Follow-up period in 9 months :

Clinical : GCS KPS

Radiological : MRI

Follow-up period in 12 months :

Clinical : GCS KPS

Radiological : MRI

Appendix – ii

Patient Information Sheet
(For the patients / respondents)

Please read the handout in front of patient / respondent and explain in local language and understandable way)

1. About the study

I have decided to do a study to see the clinical study on Role of Steroid in the treatment of chronic subdural hacmatoma. I want to include you as a study participant after receiving a written consent from you. I will expain you in a moment what are the components and your role in the study.

2. Purpose of the research

The study seeks to investigate and identify the Role of steroid in the treatment of chronic subdural hacmatoma. The results can help adopt more effective strategies for the Role of steroid in the treatment of chronic subdural hacmatoma in the region and consequently reduce CSDH.

3. Confidentiality

The information that I collect from this research project will be kept confidential unless permitted by you. Information that will be collected from this study will be used only for research purpose only. Your personal information will not be disclosed to anyone other than the investigators.

4. Right to refuse or withdraw

You have all the right to refuse to participate in this study if you do not wish to do so, and refusing to participate will not affect your treatment in any way. You may stop participating in this study at any time you wish without showing any reason and without losing any of your rights as a patient here.

5. Incentives

You will not be provided any incentives to take part in the research.

6. Risks and discomforts

There is a slight risk that you may share some personal and confidential information by chance or that you may feel uncomfortable about some of the topics. However, I do not wish this to happen, and you may refuse to any question or not take part any portion of question.

7. Benefits :

There will be no direct benefit to you, but your participation is likely to help us find out more about the disease and may be of benefit to other patients.

8. Procedure of research

If you agree, I will enroll you as a study participant and will adopt the following procedures for your participation-

i. I will take signature / thumb impression in the attached consent form in duplicate and a copy will be returned to you.

ii. I will ask you some questions and fill out a printed questionnaire.

iii. I will record the results of the laboratory investigations done.

If you agree to participate in the study, please sign this form.

_____ _____

Signature of participant Signature of Investigator

_____

Signature of whiteness

Appendix – iii

গবেষণা
রোগী সম্পর্কিত তথ্যাবলি
(রোগী / রোগীর পক্ষে জবাবদানকারী)

(অনুগ্রহ করে এই জ্ঞানপত্রটি রোগী/রোগীর পক্ষে জবাবদানকারীর নিকট পড়ে শুনান এবং স্থানীয় ভাষায় সুস্পষ্ট ভাবে বুঝিয়ে বলুন)

১। গবেষণার বিষয় ঃ
ইতোমধ্যেই জেনেছেন যে, আপনি / আপনার রোগী "ক্রনিক সাবডুরাল হেমাটোমা" রোগে ভুগছেন। আমি ঢাকা মেডিকেল কলেজ হাসপাতালে ক্রনিক সাবডুরাল হেমাটোমা রোগীর চিকিৎসায় স্টেরয়েড এর ভূমিকার উপর গবেষণা করছি। উক্ত গবেষণা আমি আপনাকে / আপনার রোগীকে লিখিত সম্মতিক্রমে অন্তর্ভূক্ত করতে চাই। আমি আপনাকে সমস্ত গবেষণা পদ্ধতিটি এবং আপনার ভূমিকা ব্যাখ্যা করবো।

২। গবেষণার উদ্দেশ্য ঃ
ক্রনিক সাবডুরাল হেমাটোমা রোগীর চিকিৎসায় স্পেরয়েড এর ভূমিকা নিরুপন একটি জটিল প্রক্রিয়া। রোগ নির্ণয়ে বিলম্ব, বহুবিধ উপসর্গের প্রকাশ ইত্যাদি কারণে রোগীর নানারূপ জটিলতা দেখা দেয়। উপসর্গের প্রকৃতি দেখে অনেক সময় এই রোগটি নির্ধারণ করতে হয়। উক্ত গবেষণায় আমরা ক্রনিক সাবডুরাল হেমাটোমা রোগীর চিকিৎসায় স্টেরয়েড এর ভূমিকা জানার চেষ্টা করবো। এর জন্য আপনার / আপনার রোগীর কিছু পরীক্ষা / নিরীক্ষার প্রয়োজন হবে, যা আপনাকে বিশদভাবে ব্যাখ্যা করে লিখিত সম্মতি সাপেক্ষে পরিচালনা করা হবে।

৩। গোপনীয়তা ঃ
এ গবেষণা থেকে সংগৃহীত তথ্যাবলি সম্পূর্ণ গোপন রাখা হবে। এ তথ্যাবলি কেবলমাত্র গবেষণার কাজেই ব্যবহার করা হবে। আপনার ব্যক্তিগত তথ্যাদি গবেষণাকারী ছাড়া অন্য কারও নিকট প্রকাশ করা হবে না।

৪। প্রত্যাখ্যান বা প্রত্যাহারের অধিকার ঃ
আপনি ইচ্ছা করলে গবেষণায় অংশগ্রহণ নাও করতে পারেন বা যে কোন মুহূর্তে আপনার সম্মতি প্রত্যাহার করতে পারেন। আপনার এই প্রত্যাহার / প্রত্যাখ্যান আপনার চিকিৎসার উপর কোনরূপ প্রভাব ফেলবে না।

৫। সুবিধা ঃ
এই গবেষণায় অংশগ্রহণের জন্য কোনরূপ আর্থিক সুবিধার ব্যবস্থা নেই। কিন্তু গবেষণার প্রয়োজনে আপনাকে আসতে হলে সেজন্য ন্যূনতম সম্মানী এবং যাতায়াত ভাতা প্রদান করা হবে।

৬। ঝুঁকি ও অসুবিধা ঃ
এই সমীক্ষায় আপনার ব্যক্তিগত ও গোপনীয় তথ্য আমাদের কাছে প্রকাশের প্রয়োজন হতে পারে এবং কিছু বিষয়ে অস্বস্তিবোধও করতে পারেন। তথাপি এরূপ পরিস্থিতি হোক আমরা তা চাই না। প্রয়োজন বোধে আপনি যে কোন প্রশ্ন বা প্রশ্নের অংশবিশেষ উত্তরদান থেকে বিরত থাকতে পারবেন।

৭। উপকারিতা ঃ

আপনি হয়ত এই সমীক্ষায় অংশগ্রহণে সরাসরি লাভবান হবেন। রোগ নির্ণয়ের পর আপনার চিকিৎসার ব্যবস্থা এই হাসপাতালেই হবে। তথাপি আপনার অংশগ্রহণে আমরা এই রোগ সম্পর্কে অনেক তথ্য পেতে পারি যা দেশে অন্যান্য চিকিৎসা ব্যবস্থায় উপকারে আসবে।

৮। গবেষণার পদ্ধতি ঃ

আপনি সম্মতি হলে আপনাকে এই সমীক্ষায় অংশগ্রহণকারী হিসেবে তালিকাভুক্ত করা হবে। আপনার অংশগ্রহণের পদ্ধতি নিম্নরূপ :

ক. সংযুক্ত ২(দুই) কপি সম্মতিপত্রে আমরা আপনার স্বাক্ষর / টিপসই নিয়ে ১(এক) কপি আপনাকে ফেরত দেয়া হবে।

খ. আমরা আপনাকে কিছু প্রশ্ন করে মুদ্রিত প্রশ্নমালায় তা পূরণ করবো।

গ. এই গবেষণার স্বার্থে আপনাকে শারীরিক পরীক্ষা করা হবে।

ঘ. এই হাসপাতাল ল্যাবরেটরিতে যে সমস্ত পরীক্ষা করা হয়েছে তার ফলাফল লিপিবদ্ধ করা হবে।

আপনি যদি এই সমীক্ষায় অংশগ্রহণে রাজী থাকেন তবে অনুগ্রহপূর্বক এই সম্মতিপত্রে স্বাক্ষর করুন।

Appendix-iv

Trials. 2017; 18: 252.

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Steroids in chronic subdural hematomas (SUCRE trial): study protocol for a randomized controlled trial

Pierre-Louis Henaux,[1,4] Pierre-Jean Le Reste,[1,4] Bruno Laviolle,[2,3,4] and Xavier Morandi[1,4]

Author information · Article notes · Copyright and License information Disclaimer

Associated Data

Data Availability Statement

Not applicable.

Abstract

Go to:

Background

Chronic subdural hematoma is a common neurological pathology, especially in older patients. The actual "gold standard" of treatment is surgical evacuation, with various techniques used across neurosurgical teams. Over the years, there has been growing evidence that inflammatory processes play a major role in the pathogenesis of CSDH. In that context, the use of corticosteroids has been proposed alone or as an adjuvant treatment to surgery. However, this practice remains very empirical and there is a need for high-quality-of-evidence studies to clarify the role of corticosteroids in the management of CSDH.

PhD

1st Seminar

ROLE OF STEROID IN THE TREATMENT OF CHRONIC SUBDURAL HAEMATOMA

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PhD STUDENT

Registration : 222/2011-12

Re-Registration : 287/2016-2017

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INTRODUCTION

- Neurosurgeons are familiar with chronic subdural haematoma (CSDH), a well-known clinical entity, which is usually treated by some modality of trepanation.
- Despite the excellent outcomes obtained by surgery, complications may occur, some of which may be potentially severe or fatal.
- Furthermore, up to 25% recurrence rate is reported. I want to present a novel approach for the management of CSDH based on the use of dexamethasone as the treatment of choice in the majority of cases.[1]

Contd …….

- Chronic subdural haematoma (CSDH) is a well-defined clinical condition consisting in a slowly progressive accumulation of liquefied blood within the subdural space.
- Such collection may, eventually, produce hemisphere compression and result in ultimate brain herniation.
- It is diagnosed in one or two persons in every 100000 in the general population per year.[2,3]
- The incidence is higher in the elderly (up to 58 per 100000 in people older than seventy), and in patients with a history of alcohol abuse or coagulation disturbance.[4]

Contd …….

- Minor head trauma a few weeks before presentation is a common antecedent. Slow venous bleeding and the creation of neo-membranes around the subdural clot are some recognized pathogenic features in the development of CSDH.[4]
- Neurosurgeons around the globe are familiar with this condition and many of them consider symptomatic CSDH a clinical scenario that requires prompt specialized evaluation and neurosurgical intervention, often on an emergency basis.
- At present, burr-hole or twist-drill craniostomy and drainage are the most widely used surgical techniques.[5]
- Neurological outcome after surgical evacuation of CSDH is known to be remarkably favourable in the great majority of patients.[6,7]

Contd …….

- Nevertheless, wound infection, subdural empyema, tension pneumocephalus, brain contusion, subdural or epidural haematoma, intracerebral haemorrhage, catheter penetration of the brain and even death may occur after surgery.[6]
- Additionally, up to 25% of patients need to be re-operated on due to re-accumulation of blood.[2]
- Surprisingly, despite this tendency towards recurrence and its related morbidity, prognosis in CSDH seems to be more influenced by the age of the patient and his/her presenting neurological status than by the type of intervention performed.[8]

Contd …….

- Thus, for adequate evaluation and analysis of outcome, it is appropriate to classify patients according to functional clinical scales such as Markwalder's grading score (MGS).[9]
- Nonoperative measures, such as, hypertonic or hyperosmolar solutions and systemic glucocorticoids have been used in CSDH with favourable results .[3]
- Systemic steroid therapy has been used in CSDH as an alternative to surgical evacuation in selected patients. The rationale for its use lies on the complex effects of corticoids over the clot membrane and neovascularization.[11]

Rationale of the Study :

- The rationale for the use of dexamethasone in CSDH lies in its anti-angiogenic properties over the subdural clot membrane, impede the formation of neomembrans & neocapillaries by their powerful inhibition of inflammatory mediators such as lymphokins & PG & stimulation of inflammatory inhibitors like lipocortin.
- Dexamethasone induce the secretion of the inhibitor of plasminogen, a substance that reduces the cycle rebleeding – lysis of the clot & reduce the expression of VEGF which inhibits abnormal angiogenesis.

Contd.....

- Dexamethasone is a feasible treatment that positively compares to surgical drain. It avoided two thirds of operations.
- The natural history of CSDH allows a 48-72 hours dexamethasone trial-
  - Without putting the patient at risk of irreversible deterioration:
  - Eliminates all morbidity related to surgery & recurrences.
  - Does not provoke significant morbidity itself.
  - Reduces hospital stay.
  - Does not preclude ulterior surgical procedures.
  - It is well tolarated & understood by the patient & relatives.
  - Reduces Cost.

Contd.....

- So we propose a protocol that does not intend to substitute surgery but offer a safe & effective alternative.
- Although few studies has been done in this topic globally. No such study in Bangladesh has been documented.
- More over this study will provide scenario of the outcomes of role of steroid in the treatment of CSDH in a tertiary hospital (DMCH) of Bangladesh which may be a future reference for further study and improve the outcome & will be helpful in framing the national strategy.

Prevalence

- Peak incidence: 6th and 7th decade of life.
- Male: Female: 2:1
- Morbidity rates: 11%
- Mortality rates: 5%

Pathophysiology

- CSDH are more common in-
  - Cerebral atrophy in old age.
  - Dementia.
  - Alcoholism.
- CSDH associated with-
  - Impaired coagulation of blood.
  - Repeated minor head injuries.
  - In younger persons: the focal cerebral atrophy associated with an arachnoid cyst.
  - Ventricular and lumber drains & lumber punctures:
    - Drop the intraventicular pressure.
    - Open up the subdural space.
    - Predispose patients to CSDH.

Contd....

- The stretched bridging veins (Between the dura mater & arachnoid mater) easily torn as a result of minor trauma, leading to hemorrhage in the subdural space.
- One day after hemorrhage:
  - Outer surface of the hematoma covered by a thin layer of fibrin & fibroblasts.
  - Blood in the subdural space triggers inflamation.
- On the 4th day after hemorrhage:
  - Migration & proliferation of the fibroblast leads to –
    - Formation of neomembrane with fragile neocapillaries.

Contd....

- During the next two weeks:
  - Further microbleeding.
  - The outer membrane progressively enlarges.
  - The fibroblasts invade the haematoma & form a thin membrane.
- Liquefaction of the haemtoma occurs due to the presents of phagocytes.
- The haemtoma either reabsorb spontaneously or slowly increase in size resulting in CSDH.
- Signficantly higher levels of-
  - Proinflamatory mediators (Interleukin-2, 5, 6, 7) &
  - Anti-inflamatory mediators.

Contd....

- Evoke a local aseptic inflamatory & inflamation induced angiogenic reaction.
- Angiogenic reaction leads to formation of neomembranes cause repeated microbleeds into the hematoma cavity.

Contd….

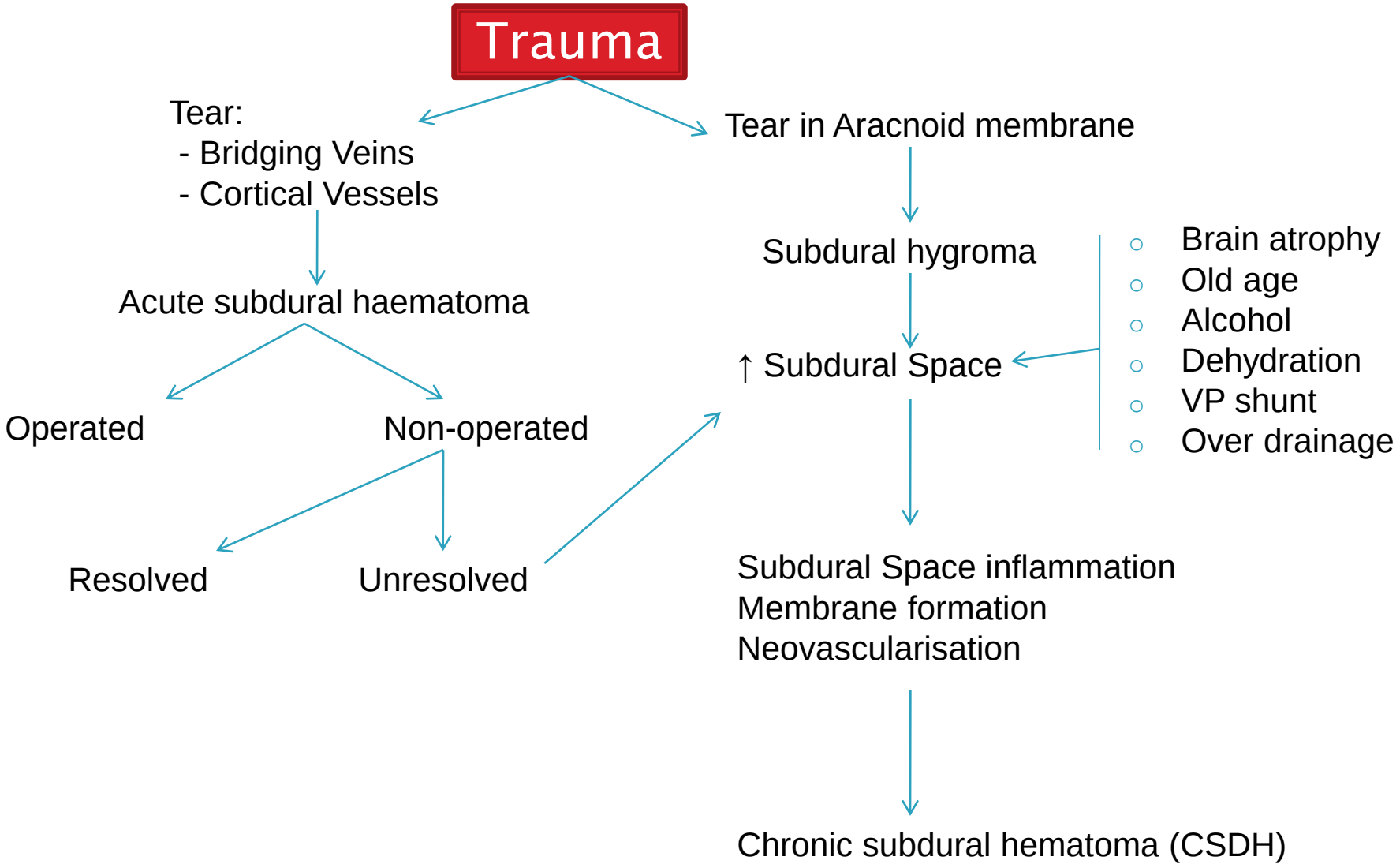


Fig: Flow chart of CSDH

Risk factors:

- Alcoholism
- Dementia
- Cerebral atrophy
  - ↑ Space between brain & the skull
  - Stretching the bridging veins & making them more vulnerable to trauma.
- 5^{th} & 6^{th} decade of life
- Head injury
- Anti coagulants or antiplatelet drugs (Aspirin)
- Bleeding tendencies
- Epilepsy
- Patient with CRF
- Warfrain
- Shunts (Cause low ICP)
- HTN
- Atherosclerosis

Clinical Manifestatins, Signs & Symptoms:

1. Altered mental state
    * Confusion
    * Drowsiness
    * Coma
2. Focal neurological deficit:
    * Weekness of the limbs (Contralateral/Ipsilatral)
3. Headache with vomiting
4. Recurrent falls
5. Seizures
6. Papilloedema
7. Extensor plantar response
8. Dysphagia
9. Neck Stiffness
10. Hemianopia
11. Dysarthria
12. Gait abnormality
13. Vertigo

Contd…

14. Nystagnus
15. Oculomtor Palsy
16. ↑ ICP
17. Gerstmann's Syndrome
    - Right-left disorientation
    - Finger agnosia
    - Agraphia &
    - Acalculia

Presentation:

1. Headache
2. Nausea
3. Vomiting
4. Impaired level of conciousness
5. Papilloedema
6. Hemiplegia
7. Dysphagia
8. Seizures
   - Focal
   - Generalized

Investigations:

CT Scan is the gold standard to make the diagnosis of CSDH.

Three Phases:

1. Hyperdense (0-7 Days)
2. Isodense (1-3 weeks)
3. Hypodense (> 3 weeks)

Treatment

a) Surgical:

- Single or double twist-drill mini craniostomy over the affected hemisphere
- Patient position: Supine
- Anaesthesia: Local & mild sedation or G/A
- 5-6 mm diameter manual drill to create a small burr hole.
- A ventricular catheter is inserted in the subdural space.
- Drainage is maintained 48-72 hours.

Contd…

b) Medical Treatment:

Dexamethasone Protocol :

- Dexamethasone 4mg 8 hourly either oral or intravenous for 21 days.
- Omeprazole 20mg 12 hourly.
- Prophylaxis of thrombophlebitis:
  - Subcutaneous enoxaparin 20-40mg per day
  - Lower limbs pneumatic compression device
- Patients neurological status is checked everyday
- Patients not improving their MGS are proposed for the surgical protocol.
- Dexamethasone is slowly tapered : 1mg per day every 3 days for 4 weeks.
- Clinical & radiological evaluation performed after 6 weeks in OPD until complete cure.

Mechanism of action of Corticosteroids (Dexamathasone)

- Corticosteroids inhbit the synthesis of-
  - Various proinflammatory mediators (Interleukin-2,5,6 & 7)
  - Immune system cells
  - Proinflammatory enzymes
  - No &
  - Cyclooxygenase
- Corticosteroids Suppresed-
  - Vascular endothelial growth factor (VEGF)
- Corticosteroids Stimulate inflammatory inhibitors like-
  - Lipocortin – which blocks phospholipase A2 & ACE
- VEGF, ACE, inflammatory & angiogenic mediators play a crucial role in the pathogenisis & maintanance of CSDH.
- Corticosteroids causes inhibition of inflammatory & angiogenetic factors → Reduce or even disrupt the information induced angiogenic reaction in CSDH.

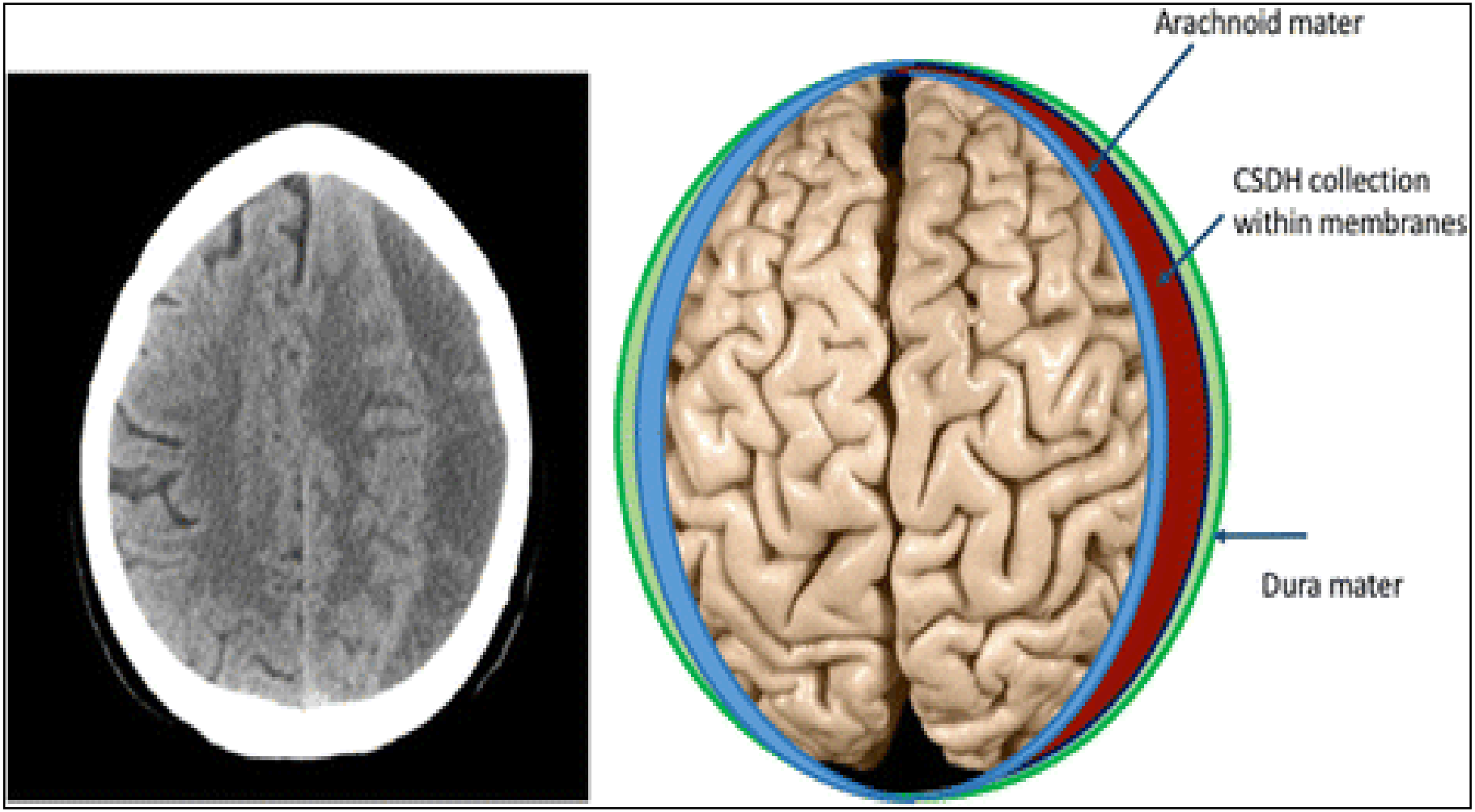


Fig: CSDH collection within membranes

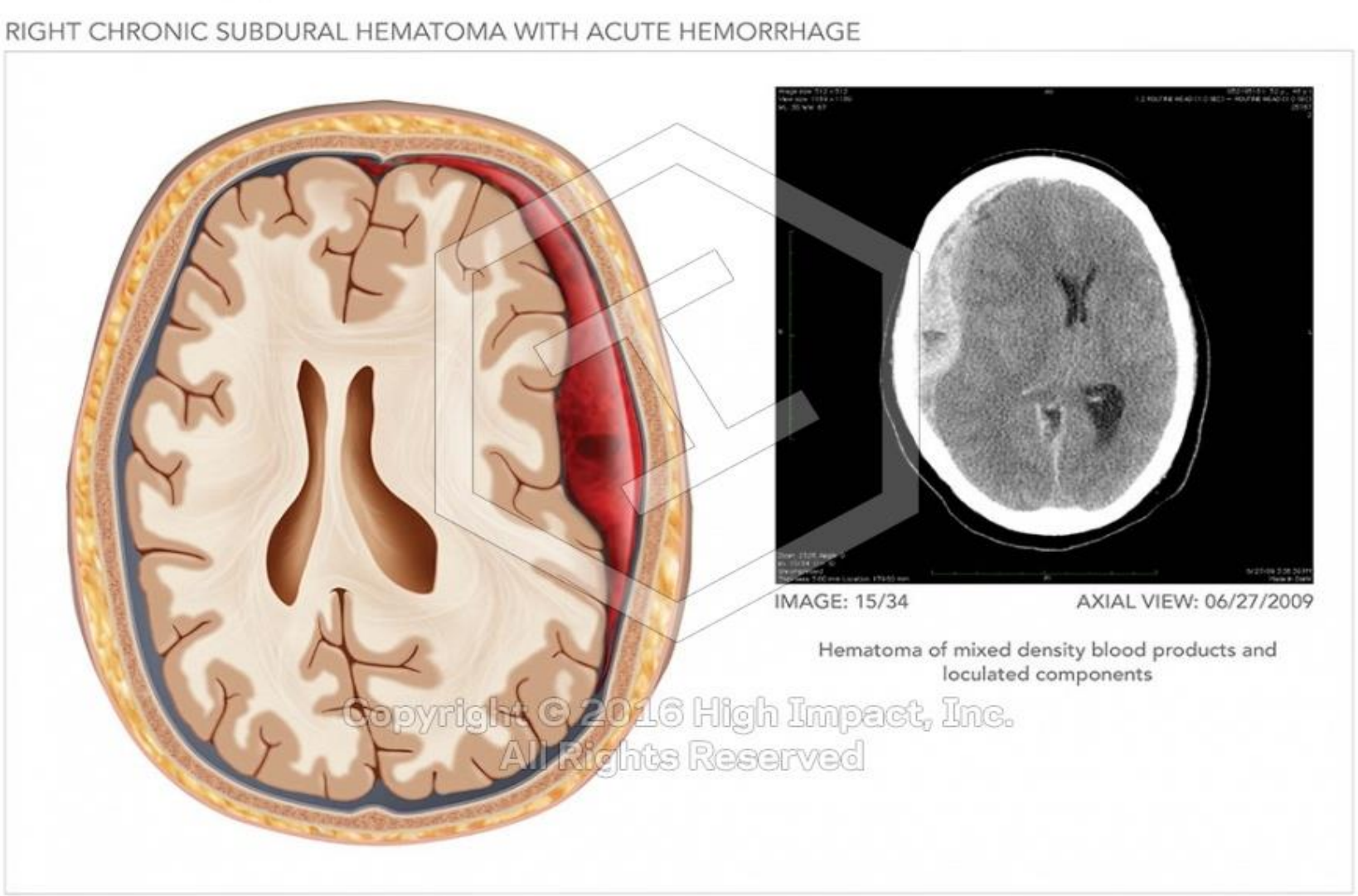


Fig: Right Chronic Subdural Hematoma

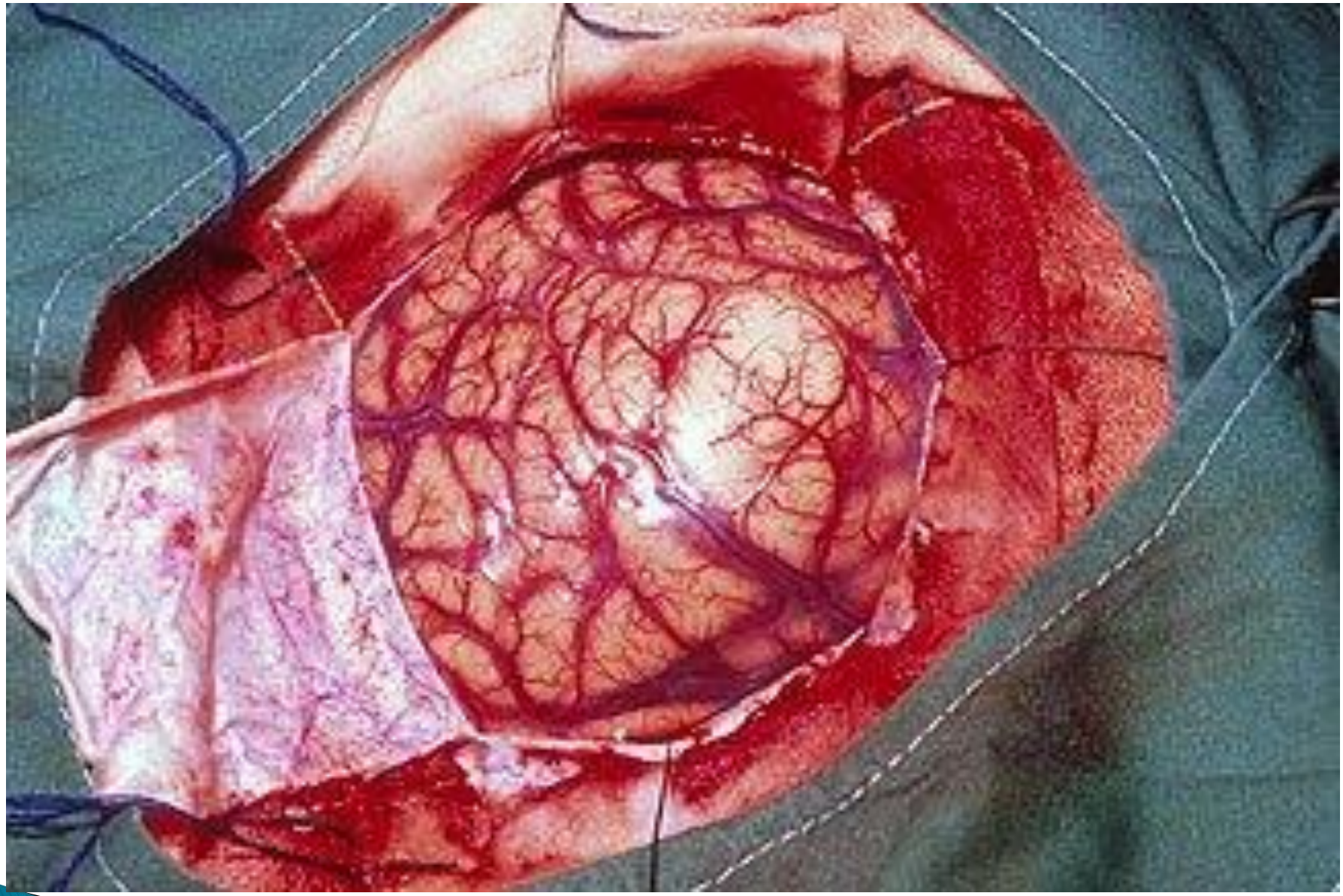
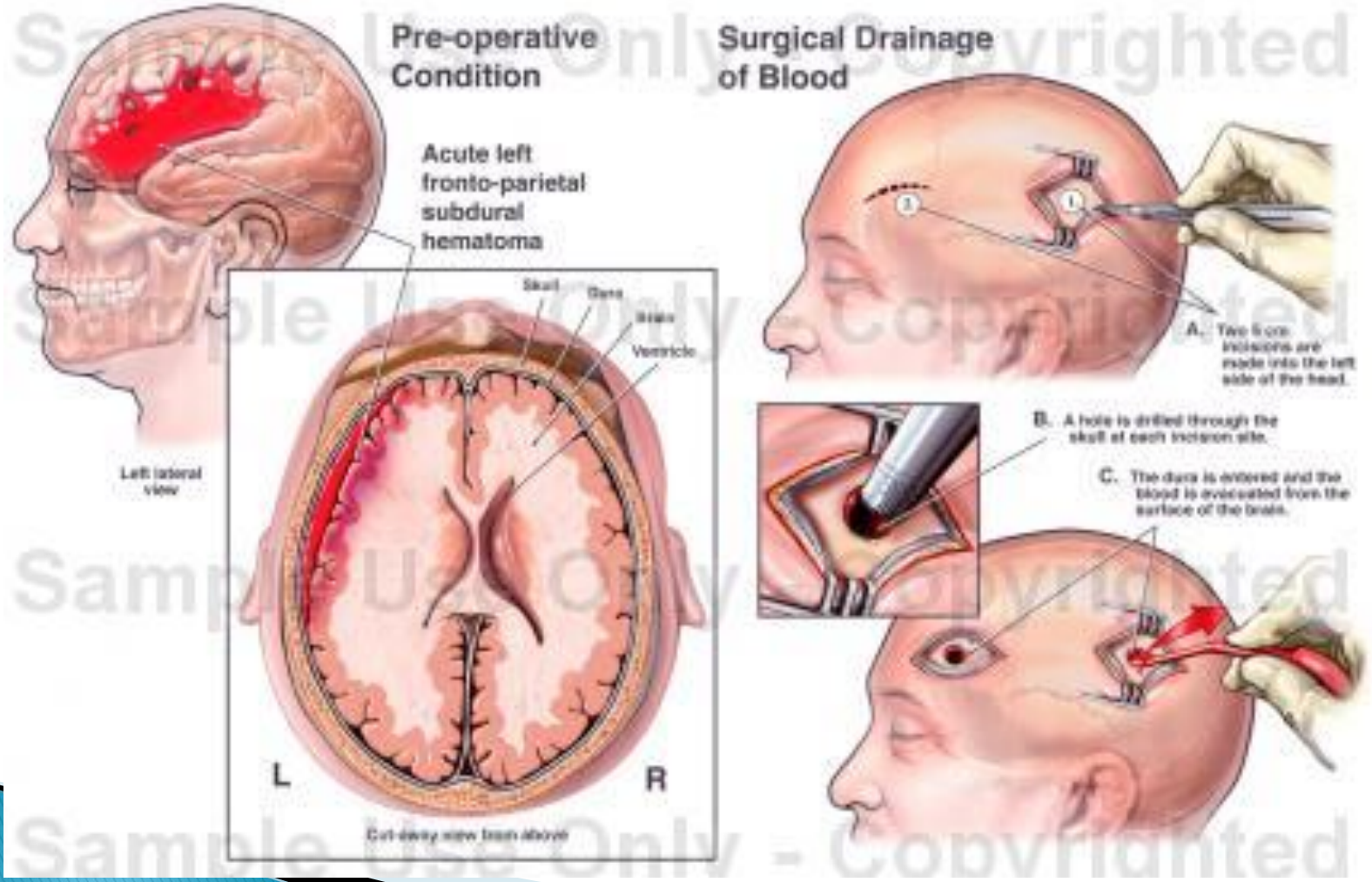


Fig: Surgical Bur hole Drainage Operation for CSDH

Brain Surgery - Brain Hemorrhage with Surgical Bur Hole Drainage



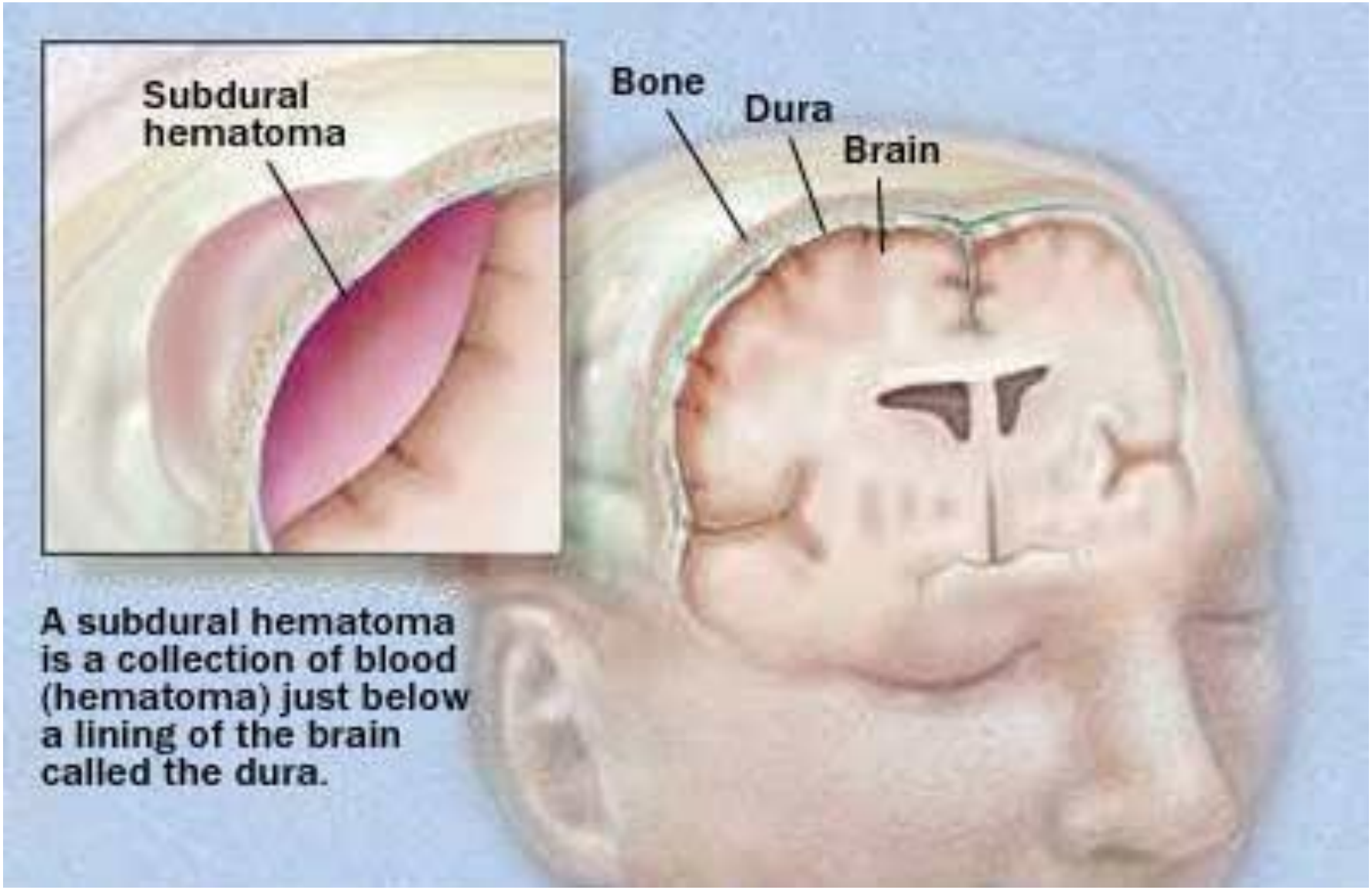


Fig: Subdural Hematoma

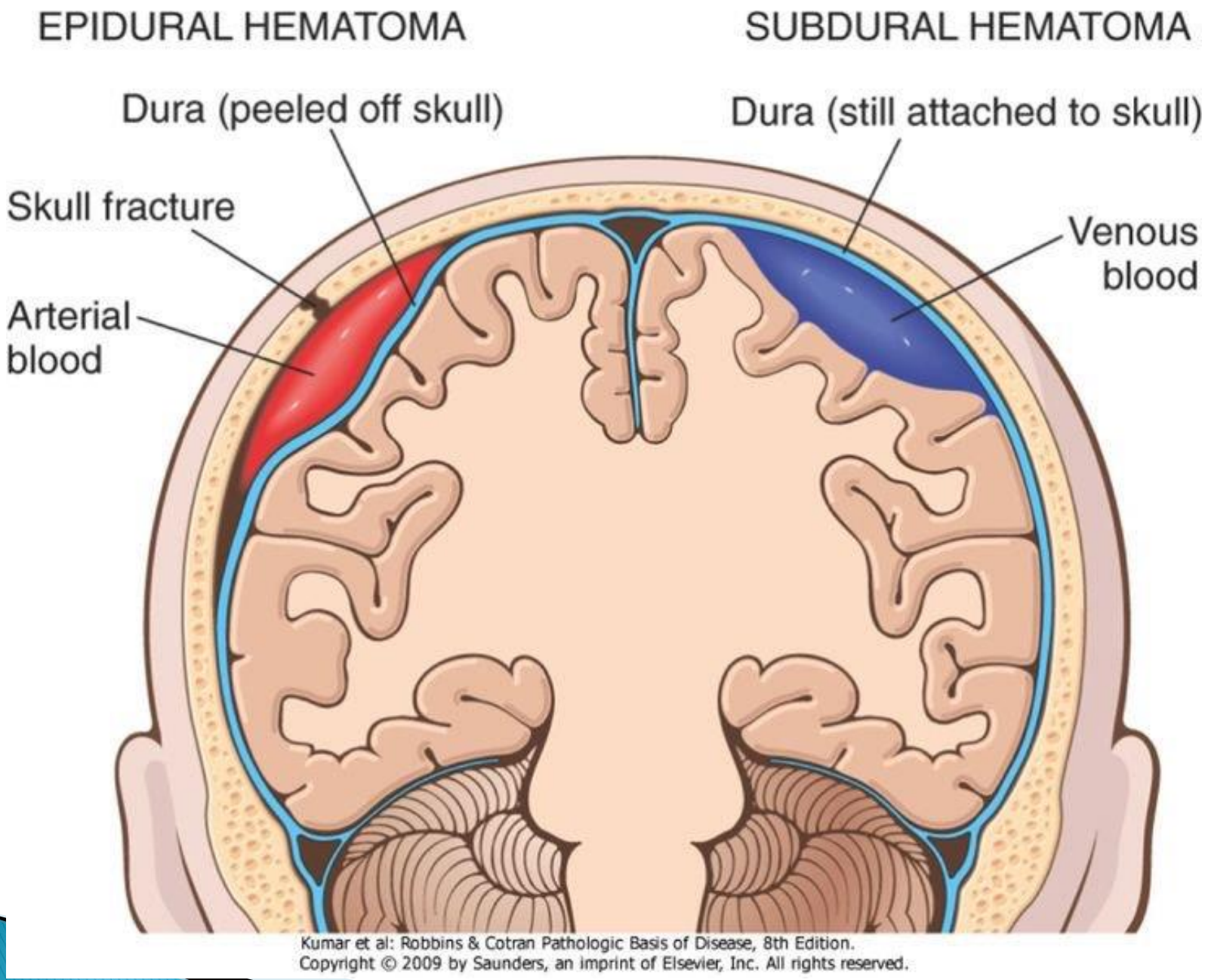


Fig: Subdural Hematoma & Epidural Hematoma

Classification of Corticosteroids

Corticosteroid	Equivalent dose (mg)	Glucocorticoid potency	Mineralocorticoid potency	Plasma half- life (minutes)	Biological half-life (hours)
Short Acting					
Cortisone	25	0.8	2+	30-90	8-12
Hydrocortisone	20	1	2+	60-120	8-12
Deflazacort	6			90-120	<12
Intermediate Acting					
Prednisone	5	4	1+	60	24-36
Prednisolone	5	4	1+	115-212	24-36
Methylprednisolone	4	5	0	180	24-36
Triamcinolone	4	5	0	78-188	24-36
Long Acting					
Dexamethasone	0.75	20-30	0	100-300	36-54
Betamethasone	0.6-0.75	20-30	0	100-300	36-54

Published studies on corticotherapy for CSDH

Authors	N	Outcome & Comments
Rudiger A et al (2001)23	1	Dexamethasone 4mg/12 hours. Seventy-six year-old diabetic patient presenting with confusion and ataxia, harbouring a bilateral CSDH. Surgery impossible because of anaesthetic problems. Developed hyperglycaemic impairment that needed insulin therapy. Resolved completely in a few days. CT image normal alter 6 weeks.

Published studies on corticotherapy for CSH CONTD….

Authors	N	Outcome & Comments
Decaux O et al (2002)3	02	Cortancyl® (cortisone 1mg/Kg/day). Complete early clinical and radiological resolution.
Sun TFD et al (2005)26	26	Dexamethasone 4mg/6h for 21 days. Patients in old age with medical co-morbidity or who refused surgical treatment. Twenty-three patients (84%) achieved favourable outcome. Surgical drain plus steroids reduced the chance of re-accumulation.

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Associated Data

Data Availability Statement

Not applicable.

Abstract

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Background

Chronic subdural hematoma (CSDH) is a common neurological pathology, especially in older patients. The actual "gold standard" of treatment is surgical evacuation, with various techniques used across neurosurgical teams. Over the years, there has been growing evidence that inflammatory processes play a major role in the pathogenesis of CSDH. In that context, the use of corticosteroids has been proposed alone or as an adjuvant treatment to surgery. However, this practice remains very empirical and there is a need for high-quality-of-evidence studies to clarify the role of corticosteroids in the management of CSDH.

The role of corticosteroids in the management of chronic subdural hematoma: A systematic review

Article · Literature Review *in* European Journal of Neurology 19(11):1397-403 · May 2012 *with* 934 Reads
DOI: 10.1111/j.1468-1331.2012.03768.x · Source: PubMed

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Abstract

The role of corticosteroids in the management of chronic subdural hematoma (CSDH) remains a matter of debate. Standard surgical treatment has recurrence rates reported between 4 and 26%. We reviewed the safety and effectiveness of corticosteroids both as a monotherapy and as an adjunct to surgery in patients with CSDH. PubMed-MEDLINE, EMBASE and Cochrane databases were searched in July 2011 for randomized controlled trials and for prospective and retrospective cohort studies, reporting on 10 or more adult patients with CSDH. Quality was assessed according to the STROBE checklist. Corticosteroid monotherapy and surgery with corticosteroids as an adjunct were compared with no treatment or surgery only, with regard to lethality, neurological outcome, secondary intervention and complications. Five observational studies were included in this review. There was no randomized allocation of treatment in any study. Secondary intervention rates ranged from 3 to 28%, lethality rates ranged from 0 to 13%, and good outcome was seen in 83–100%. Hyperglycemia occurred more often in patients treated with corticosteroids. In only two studies, one case of gastrointestinal bleeding was observed. Five observational studies suggest that corticosteroids might be beneficial in the treatment of CSDH; however, there is a lack of well-designed trials that support or refute the use of corticosteroids in CSDH. These results encourage further randomized clinical trials to establish the role of corticosteroids in CSDH.

Neurocirugía
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Dexamethasone treatment in chronic subdural haematoma

P.D. Delgado-López; V. Martín-Velasco; J.M. Castilla-Díez; A. Rodríguez-Salazar; A.M. Galacho-Harriero y O. Fernández-Arconada

Servicio de Neurocirugía. Hospital General Yagüe. Burgos.

Summary

***Introduction*. Neurosurgeons are familiar with chronic subdural haematoma (CSH), a well-known clinical entity, which is usually treated by some modality of trepanation. Despite the excellent outcomes obtained by surgery, complications may occur, some of which may be potentially severe or fatal. Furthermore, up to 25% recurrence rate is reported. The authors present a novel approach to the management of CSH based on the use of dexamethasone as the treatment of choice in the majority of cases.**

***Patients and methods*. Medical records of 122 CSH patients were retrospectively reviewed. At admission, symptomatic patients were classified according to the Markwalder Grading Score (MGS). Those scoring MGS 1-2 were assigned to the Dexamethasone protocol (4mg every 8h, re-evaluation after 48-72h, slow tapering), and those scoring MGS 3-4 were, in general, assigned to the Surgical protocol (single frontal twist-drill drainage to a closed system, without irrigation). Patients were followed in the Outpatient Office with neurological assessment and serial CT scans.**

***Results*. Between March 2001 and May 2006, 122 consecutive CSH patients (69% male, median aged of 78, range 25-97) were treated. Seventy-three percent of the patients exhibited some kind of neurological defect (MGS 2-3-4). Asymptomatic patients (MGS 0) were left untreated. Initial treatment assignment was: 101 dexamethasone, 15 subdural drain, 4 craneotomy and 2 untreated. Twenty-two patients on dexamethasone ultimately required surgical drain (21.8%). Favourable outcome (MGS 0-1-2) was obtained in 96% and 93.9% of those treated with dexamethasone and surgical drain, respectively. Median hospital stay was 6 days (range 1-41) for the dexamethasone group and the whole series, and 8 days (range 5-48) for the surgical group. Overall mortality rate was 0.8% and re-admissions related to the haematoma reached 14.7% (all maintained or improved their MGS). Medical complications occurred in 34 patients (27.8%), mainly mild hyperglycemic impairments. Median outpatient follow up was 25 weeks (range 8-90), and two patients were lost.**

***Discussion*. The rationale for the use of dexamethasone in CSH lies in its anti-angiogenic properties over the subdural clot membrane, as it is derived from experimental studies and the very few clinical observations published. Surgical evacuation of CSH is known to achieve excellent results but no well-designed trials compare medical versus surgical therapies. The experience obtained from this series lets us formulate some clinical considerations: dexamethasone is a feasible treatment that positively compares to surgical drain (and avoided two thirds of operations); the natural history of CSH allows a 48-72h dexamethasone trial without putting the patient at risk of irreversible deterioration; eliminates all morbidity related to surgery and recurrences; does not provoke significant morbidity itself; reduces hospital stay; does not preclude ulterior surgical procedures; it is well tolerated and understood by the patient and relatives and it probably reduces costs. The authors propose a protocol that does not intend to substitute surgery but to offer a safe and effective alternative.**

***Conclusion*. Data obtained from this large retrospective series suggests that dexamethasone is a feasible and safe option in the management of CSH. In the author's experience dexamethasone was able to cure or improve two thirds of the patients. This fact should be confirmed by others in the future. The true effectiveness of the therapy as compared to surgical treatment could be ideally tested in a prospective randomized trial.**

KEY WORDS: Chronic subdural haematoma. Dexamethasone. Nonoperative treatment. Glucocorticoids.

Tratamiento con dexametasona del hematoma subdural crónico

Recibido: 4-08-07. Aceptado: 23-01-09

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Trials

STUDY PROTOCOL Open Access

Steroids in chronic subdural hematomas (SUCRE trial): study protocol for a randomized controlled trial

Pierre-Louis Henaux[1,4*], Pierre-Jean Le Reste[1,4], Bruno Laviolle[2,3,4] and Xavier Morandi[1,4]

Abstract

Background: Chronic subdural hematoma (CSDH) is a common neurological pathology, especially in older patients. The actual "gold standard" of treatment is surgical evacuation, with various techniques used across neurosurgical teams. Over the years, there has been growing evidence that inflammatory processes play a major role in the pathogenesis of CSDH. In that context, the use of corticosteroids has been proposed alone or as an adjuvant treatment to surgery. However, this practice remains very empirical and there is a need for high-quality-of-evidence studies to clarify the role of corticosteroids in the management of CSDH.

Methods/design: We propose a double-blind, randomized controlled trial comparing methylprednisolone versus placebo in the treatment of CSDH without clinical and/or radiological signs of severity. The treatment will be administered daily for a duration of 3 weeks, at a dose of 1 mg/kg. The primary endpoint will be the delay of occurrence of surgical treatment at 1 month following the introduction of the treatment. Secondary endpoints will include the rate of recourse to surgery, survival rate, quality of life and functional assessments, occurrence of systemic secondary effects and radiological assessment of the response to treatment. This multimodal assessment will be done at 1, 3 and 6 months. Two hundred and two patients (101 per arm) are expected to be included considering our primary hypotheses.

Discussion: This trial started in June 2016; its results may open interesting alternatives to surgery in the management of patients harboring a CSDH, and may provide insights into the natural history of this common pathology.

Trial registration: ClinicalTrials.gov, ID: NCT02650609. Registered on 4 January 2016.

Keywords: Chronic subdural hematoma, Corticosteroids, Methylprednisolone, Elderly patients, Conservative treatment

Background

Chronic subdural hematoma (CSDH) is one of the most frequent neurosurgical pathologies [1, 2]. To date, it has mainly involved older patients, with an annual incidence rate of 15 cases for 100,000 persons aged over 70 years [3, 4]. Considering that the population of patients aged over 65 years old is estimated to increase three-fold by the 2030s [5], and the increasing prescription of anti-coagulant or platelet aggregation-inhibiting drugs, more and more practitioners will be confronted with this pathology which thus represents a major public health issue. Surgical evacuation of CSDH is currently the "gold standard" treatment [6]. In an often fragile population, surgical treatment carries significant morbidity at surgical (early recurrence which manifests itself in acute subdural hematoma, infections, intracerebral hematoma) as well as at medical (seizures, acute respiratory disease, urinary tract infections, confusional states, bedsore complications) levels. There is an increased mortality risk until 1 year after surgical evacuation [7], and hospital costs are high, with a very variable length of stay.

Beyond its classic traumatic etiology, the pathophysiology of CSDH involves inflammatory processes so that CSDH can now also be considered as an inflammatory disease. CSDH, therefore, appears to be a self-sustaining

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Dexamethasone treatment in chronic subdural haematoma

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Servicio de Neurocirugía. Hospital General Yagüe. Burgos.

HYPOTHESIS

- What is the role of Steroid in the treatment of chronic subdural haematoma?

OBJECTIVES

General objectives:

- To evaluate the effect of management of CSDH after treatment with steroid.

Specific objectives:

- To test the necessity of steroid in the management of CSDH.
- To assess the morbidity and mortality of CSDH following steroid management.
- To assist the outcome of the management of CSDH with or without steroid drugs
- To evaluate the recovery of the patients of CSDH with or without steroid drugs.

METHODOLOGY

Type of study:

- The study was a Randomized controlled clinical trial.

Place of study:

- This study was carried out at the Department of Neurology and Neurosurgery of Dhaka Medical College Hospital.

Duration of study:

- From July 2012 to June 2017

Study population:

- All Patients visited at emergency department of DMCH & admitted in the neurology & Neurosurgery department of DMCH having non contrast enhanced CT scan suggestion of CSDH.

Inclusion criteria:

- CSDHs diagnosed clinically and radiologically.

Clinically:

- Headache
- Behavioral disturbances.
- Vomiting
- Contra lateral limb weakness
- speech disorder
- Vertigo
- Seizure

Radiologically:

- Non- contrast CT scan of head showing chronic subdural haematoma.

CT Findings:

- There should be a hypodense / isodense / mixed dense area located just under the duration (Non- Contrast film) with evidence of midline shifting.

Exclusion criteria:

- Patients with CSDH having steroid with the following criteria was excluded from the study-
- Patient with use of antithrombolytic and anticoagulant drugs.
- Age less than 12 years.
- CT scan showing signs of acute haemorrhage or loculations or membrane formation within CSDH.

Sample size:

- A total of 60 Patients, meeting the specific criteria and was admitted during the study period in the neurology & neurosurgery department of DMCH was included in this study.
- They were equally divided into two groups. They were diagnosed as CSDH by non-contrast CT scan of head.

Sampling technique:

- Purposive sampling (randomized) according to availability of the patients and strictly considering the inclusion and exclusion criteria.

Variables:

Are discussed and considered on the basis of

Demographic and clinical variables:

- Age of the patient
- sex of the patient
- Glasgow comma scale at the presentation.

Imaging variables (CT scan related variables):

- Side and site of the haematoma
- Shifting of the midline

Medical management variables:

- Steroid given or not.

Medical outcome variables:

- Glasgow coma scale (GCS)
- Glasgow outcome scale (GOS)
- The Markwalder scale of CSDH.

Data collection procedure:

- Data was collected with a pre-tested structured questionnaire containing history, clinical and laboratory investigations.
- On admission, a detailed history of the illness was taken from the patients / patients' attendant.
- I carried out through general and neurological examinations. GCS score and Markwalder scale were determined and recorded.
- Findings of CT scan were recorded.
- Operative findings were noted and recorded in the data sheet.

Data collection:

- After enrollment of the patient, the data of the following variables was collected.

Data processing and data analysis:

- Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA).
- The mean values were calculated for continuous variables.
- The quantitative observations were indicated by frequencies and percentages.
- Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. P values <0.05 was considered as statistically significant.

Ethical consideration:

- Informed written consent was taken from the patient or patient's guardian after duly informing the procedure of treatment, anticipated result, possible advantages, disadvantages and complications considering all ethical issues.
- Confidentiality was maintained both verbally and documentary by using separate locker and computer password.
- Protocol was approved by ethical committee of Dhaka Medical College Hospital.

ঢাকা মেডিকেল কলেজ
DHAKA MEDICAL COLLEGE
Dhaka, Bangladesh

Ref: DMC/Ethical/2013/140

Date: 21/07/2013

Ethical Clearance Certificate

The Ethical Committee of Dhaka Medical College Approved the Following Research Protocol in time.

Title of the Research Work :

"Role of steroid in the treatment of chronic subdural haematoma".

Principal Investigator :
Md. Abdus Salam
Ph.D. Student,
Department of Clinical Pharmacy & Pharmacology, University of Dhaka.

Supervisor :
Prof. Dr. Md. Saiful Islam
Dean, Faculty of Pharmacy,
University of Dhaka.

Place of Study :
Department of Neurology and Neurosurgery,
Dhaka Medical College Hospital, Dhaka.

Duration :
July 2012 to June 2014.

Prof. (Dr.) K.M. Shahidul Islam
Head of the Deptt. of Microbiology &
Chairman, Ethical Review Committee,
Dhaka Medical College, Dhaka.

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Professor Dr Md Saiful Islam
B Pharm (Hons) M Pharm Ph D
Dean

No: Fa. ph-464/13 Date 20.1.2012

Departmental Ethical Clearance Certificate

The Departmental Ethical Committee of University of Dhaka. Approved the Following Research Protocol in time.

Title of the Research work:
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Principle investigator :
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Place of study: Department of Neurology and Neurosurgery of Dhaka Medical College Hospital

Duration: June 2012 - June 2014.

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নং-৪৫.১৬৮.১১৯.০৩.০০.০৮২ (অংশ-৩).২০১৩ — ৬৮৬ তারিখঃ ২৫-১১-২০১৩ খ্রিঃ

বিষয়ঃ পিএইচডি কোর্সে অধ্যয়নের জন্য অনুমতি প্রদান প্রসংগে।

সূত্রঃ ডিজিএইচএস/পার-২/এস-২৭/০৩/১৫৯০২,তারিখঃ ২৭/১০/২০১৩

উপর্যুক্ত বিষয় ও সূত্রের পরিপ্রেক্ষিতে জানানো যাচ্ছে যে, ডাঃ মোঃ আব্দুস সালাম (কোড নং-১১১৪৯১), ইমারজেন্সী মেডিকেল অফিসার, ঢাকা মেডিকেল কলেজ হাসপাতাল, ঢাকা-কে ঢাকা বিশ্ববিদ্যালয়ের ক্লিনিক্যাল ফার্মেসী ও ফার্মাকোলজি বিভাগে অধ্যাপক ড. মোঃ সাইফুল ইসলাম এর অধীনে Role of Steroid in the Treatment of Chronic Subdural Haematoma বিষয়ে পিএইচডি কোর্সে অধ্যয়নের জন্য নিম্নোক্ত শর্তে নির্দেশক্রমে অনুমতি প্রদান করা হলো:

(১) এ কোর্সে অধ্যয়নের যাবতীয় ব্যয় তিনি নিজে বহন করবেন,এতে সরকারের কোন আর্থিক সংশ্লেষ থাকবে না;
(২) এ কোর্সে অধ্যয়নের সময় সরকারী কাজের কোন ব্যঘাত সৃষ্টি করা যাবে না;
(৩) ছুটির দিনেও কোন সরকারী দায়িত্ব অর্পিত হলে তিনি তা পালনে বাধ্য থাকবেন;
(৪) জনস্বার্থে যে কোন সময় সরকার এ আদেশ বাতিল করতে পারবে;

২৫/১১/১৩
(মোঃ রেজাউল আলম)
সিনিয়র সহকারী সচিব
ফোনঃ-৯৫৪০৭৩০

মহাপরিচালক
স্বাস্থ্য অধিদপ্তর
মহাখালী, ঢাকা।

দৃষ্টি আকর্ষণঃ পরিচালক (চিকিৎসা শিক্ষা),স্বাস্থ্য অধিদপ্তর, মহাখালী, ঢাকা।

অনুলিপি সদয় অবগতি ও প্রয়োজনীয় ব্যবস্থা গ্রহণের জন্য প্রেরণ করা হলোঃ

১. পরিচালক, ঢাকা মেডিকেল কলেজ হাসপাতাল, ঢাকা।
২. অধ্যাপক ড. মোঃ সাইফুল ইসলাম, ডীন, ক্লিনিক্যাল ফার্মেসী ও ফার্মাকোলজি বিভাগ, ঢাকা বিশ্ববিদ্যালয়, ঢাকা।
৩. রেজিস্ট্রার, ঢাকা বিশ্ববিদ্যালয়, ঢাকা।
৪. ডাঃ মোঃ আব্দুস সালাম (কোড নং-১১১৪৯১), ইমারজেন্সী মেডিকেল অফিসার, ঢাকা মেডিকেল কলেজ হাসপাতাল, ঢাকা।

নং-ক্লিঃফাঃ/৭২/২০১৩-২০১৪

বরাবর

রেজিষ্ট্রার
ঢাকা বিশ্ববিদ্যালয়

মাধ্যমঃ চেয়ারম্যান, ক্লিনিকাল ফার্মেসী ও ফার্মাকোলজি বিভাগ ঢাকা বিশ্ববিদ্যালয়।

বিষয়ঃ- চাকুরীরত অবস্থায় পিএইচডি কোর্সে অধ্যয়নের আবেদন।

মহাত্মন,

সাতিশয় শ্রদ্ধান্তে সানুনয় নিবেদন এই যে, আমি ডাঃ মোঃ আব্দুস সালাম, ইমারজেন্সী মেডিকেল অফিসার হিসাবে ঢাকা মেডিকেল কলেজ হাসপাতালে কর্মরত আছি। আমি এমবিবিএস ডিগ্রী অর্জনের পর ইএমপিএইচ (ইপিডিমিওলজি) ও এমফিল (P-1) সম্পন্ন করি। বর্তমানে আমি ঢাকা বিশ্ববিদ্যালয়ে ক্লিনিকাল ফার্মেসী ও ফার্মাকোলজি বিভাগে অধ্যাপক ড. মোঃ সাইফুল ইসলাম স্যারের অধীনে "Role of Steroid in The treatment of Chronic Subdural Haematoma" এই বিষয়ের উপর পিএইচডি কোর্সে অধ্যয়ন করার সুযোগপ্রাপ্ত।

বিশ্ববিদ্যালয়ের বিজ্ঞপ্তির স্মারক নং রেজিঃ/শিক্ষা-১/৫৪৫৭২-সি অনুযায়ী "বিশ্ববিদ্যালয় বহির্ভূত চাকুরীরত এমফিল বা সমমানের ডিগ্রীধারীদের ছুটি নেওয়া বাধ্যতামূলক নয়" অনুযায়ী এবং আমার চাকুরী ও পিএইচডি গবেষনা সম্পূর্ন সামঞ্জস্যপূর্ন হওয়ায় ক্লিনিকাল ফার্মেসী ও ফার্মাকোলজি বিভাগের একাডেমিক কমিটির অনুমতি সাপেক্ষে উপরে উল্লিখিত বিশ্ববিদ্যালয়ের প্রচলিত নিয়ম অনুযায়ী ছুটি না নিয়ে চাকুরীস্থল (ঢাকা মেডিকেল কলেজ হাসপাতাল) থেকে পিএইচডি প্রোগ্রামে অধ্যয়নের অনুমতি প্রদান করা যেতে পারে সংক্রান্ত প্রত্যয়ন পত্র (আবেদনের সাথে সংযুক্ত) নিয়ে আমি পিএইচডি প্রোগ্রামে যোগদান করিতে ইচ্ছুক।

অতএব সনির্বন্ধ নিবেদন যাহাতে আমি চাকুরীরত অবস্থায় পিএইচডি কোর্সে অধ্যয়ন করিতে পারি তার বিহিত ব্যবস্থা করিতে একান্ত মর্জি হয়।

সুগোচরার্থে নিবেদক

Salam 05-09-2013
(ডাঃ মোঃ আব্দুস সালাম)
ইমারজেন্সী মেডিকেল অফিসার
ঢাকা মেডিকেল কলেজ হাসপাতাল, ঢাকা।
কোড নং-১১১৪৯১।

Recommended
MSalam
5.9.13
Dr. Md. Saiful Islam
Professor
Department of Clinical Pharmacy & Pharmacology, University of Dhaka.

২৪.১১.২০১৩ তারিখে অনুষ্ঠিত বিভাগীয় একাডেমিক কমিটির সভার সিদ্ধান্ত মোতাবেক ডাঃ মোঃ আব্দুস সালাম, ইমারজেন্সী মেডিকেল অফিসার, ঢাকা মেডিকেল কলেজ হাসপাতাল, ঢাকা-কে পিএইচডি কোর্সে অধ্যয়নের জন্য প্রস্তাবিত করা হলো।

Prof. Farida Begum
Chairman
Department of Clinical Pharmacy & Pharmacology, Faculty of Pharmacy
University of Dhaka, Bangladesh.

Faculty of Pharmacy
University of Dhaka
Dhaka-1000, Bangladesh

Professor Dr Md Saiful Islam
B Pharm (Hons) M Pharm Ph D
Dean

Date: 27-05-2013

To
Dr. Quazi Deen Mohammad
Principal
Dhaka Medical College
Professor and Head
Department of Neurology
Dhaka Medical College Hospital.

Subject: "Permission for data collection for the research tropic entitled "Role of steroid in the treatment of chronic subdural haematoma"

Dear Sir,

We are investigating the Role of steroid in the treatment of chronic subdural haematoma patients in Bangladesh. This is being conducted by one of my research student Md. Abdus Salam. Very few studies can be cited related to the entitled research topic especially no work has been done yet with Bangladeshi patients. In order to complete the study fruitfully, we need to collect data from your hospital. The collected data will be utilized only for research purpose. This study will be a useful tool for medical and pharmaceutical professionals and the people of Bangladesh will be benefited from it. For this study, your permission & cooperation to collect the data is very much essential.

I hope you would be kind enough to indicate your valuable consent and cooperate for collecting the data.

Your kind cooperation in this regard will be highly acknowledged & appreciated. Thank you very much for your kind assistance to us.

Sincerely yours

27.5.13

Professor Dr. Md. Saiful Islam
B.Pharm(Hons),M.Pharm,PhD.
Dean
Faculty of Pharmacy,
Former chairman,
Department of Clinical Pharmacy and Pharmacology
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Thanks for Patients Hearing