A RANDOMISED CONTROL TRIAL COMPARING
PLAIN ROPIVACAINE WITH ROPIVACAINE MIXED
WITH ADJUVANT DEXAMETHASONE IN SCALP
NERVE BLOCKS IN PATIENTS UNDERGOING
SUPRATENTORIAL CRANIOTOMY UNDER
GENERAL ANAESTHESIA

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INTRODUCTION
**Introduction**

Anaesthesia for neurosurgical procedures entails a prudent balance of various factors that determine intracranial tension, cerebral metabolic rate and blood supply. The prolonged duration of meticulous surgical technique, need for placement of invasive arterial and central and venous catheters, requirement of sound knowledge of various pharmacodynamics properties of anaesthetic and non-anaesthetic drugs to manipulate intracranial pressure-volume relationships present an enormous challenge to the perioperative physician.

The need for tailoring anaesthetic techniques to optimise monitoring of motor or sensory evoked potentials during surgery, cautious fluid management to minimise rise in intracranial blood volume while promptly replacing losses owing to osmotic agent-induced diuresis and blood loss as well as devising a strategy for post-operative pain management that balances optimal analgesia with minimal sedation, nausea and respiratory depression pose a tremendous task to the neuroanaesthesiologist involved in the perioperative care of the patient.

The non-uniform distribution of pain fibres in the central nervous system causes large fluctuations in blood pressure and heart rate during intracranial surgery. Since pain experienced during craniotomy and in the postoperative period are due to a large extent from the scalp and the pericranial muscles, blocking the sensory nerve fibres supplying these could reduce the total anaesthetic requirement enabling early recovery. Scalp nerve block using local anaesthetics along with mild sedation is routinely used for awake craniotomy.

This has also been studied as an adjunct for treatment of post-operative craniotomy pain and has been found to be effective in increasing the time interval between extubation and the first dose of post-operative rescue analgesic with lower pain scores similar to that of intravenous morphine.
Many pharmacological agents have been added to local anaesthetics and their efficacy to prolong the duration of analgesia have been evaluated. In this dissertation we aspire to explore the role of adding dexamethasone as an adjuvant to local anaesthetic ropivacaine in pre-induction scalp nerve blocks in patients undergoing supratentorial craniotomy for space-occupying lesions under general anaesthesia.
AIMS AND OBJECTIVES
**Aims:**

To study the effect of adding dexamethasone as adjuvant to local anaesthetic ropivacaine in scalp nerve blocks in patients undergoing supratentorial craniotomy under general anaesthesia.

**Objectives:**

1. To compare duration of post-operative analgesia afforded by addition of dexamethasone as adjuvant to local anaesthetic ropivacaine in scalp nerve blocks with plain ropivacaine in patients undergoing supratentorial craniotomy
2. To evaluate the following parameters in the patients who receive plain ropivacaine in the scalp nerve block and those who receive ropivacaine as well as dexamethasone in the scalp block:
   - intra-operative anaesthetic requirement
   - time to emergence from general anaesthesia
   - incidence of post-operative nausea and vomiting

**Hypothesis:**

Addition of dexamethasone to ropivacaine in scalp nerve blocks given to patients undergoing supratentorial craniotomy under general anaesthesia prolongs the duration of post-operative analgesia, decreases intra-operative anaesthetic requirement, shortens time to emergence from general anaesthesia and decreases post-operative nausea and vomiting.
REVIEW OF LITERATURE
Review of Literature

1. Introduction to Neuroanaesthesia

2. History of Local Anaesthesia in Craniotomies

3. Anaesthetic Concerns in Supratentorial Craniotomies

4. Post-operative Pain Management in Supratentorial Craniotomies: Modalities and Challenges

5. Scalp Nerve Block: Anatomy, Techniques, Complications, Efficacy

6. Dexamethasone: a novel adjuvant to local anaesthetics in peripheral nerve blocks

7. Pre-operative Pain Assessment: Methods, Role in Predicting Post-operative Analgesic Requirement

1. **Introduction to Neuroanaesthesia:**

   Anaesthesia for neurosurgical procedures requires a sound knowledge of cerebral and spinal cord anatomy, blood supply and metabolism, effects of anaesthetic agents on intracranial pressure and cerebral blood flow as well as awareness of modern neuroradiology and neurophysiological monitoring techniques pertinent to management of specific cases. Neurosurgical procedures range from burr hole drilling for evacuation of extradural hematomas to more intricate surgeries involving excision of supra- and infratentorial mass lesions, clipping of cerebral aneurysms, resection of arteriovenous malformations, awake craniotomy for epilepsy surgery, management of head injury patients, interventional neuroradiology and robotic surgery.
Tumours involving the central nervous system, though uncommon, are not a rare entity in clinical practice. More than 80% of brain tumours in adults are supratentorial, the commonest being gliomas (36%), meningiomas (32.1%) and pituitary adenomas (8.4%). Approximately half of the tumours are malignant. The five most common sources of brain metastases are breast, colorectal, kidney, lung and melanoma. As there is no organised brain tumour registry in India, it is difficult to obtain robust epidemiologic data for the country. Age-adjusted incidence rate of primary brain tumours in India is 3.9 per 100,000 population for males and 2.4 per 100,000 population for females, with a male preponderance for all histological classifications.

Anaesthetic management of supratentorial brain tumours requires an understanding of the pathophysiology of local or generalized rising intracranial pressure, regulation and maintenance of cerebral perfusion and how to avoid secondary systemic insults to the brain. These secondary insults to the already injured brain may be local or systemic: local insults include further rise of intracranial pressure, tearing of cerebral vessels by midline shift, epilepsy and vasospasm; systemic insults include hypercapnia, hypoxemia, hypotension or hypertension, hypo- or hyperosmolality, hypo- or hyperglycaemia and hyperthermia.

2. **History of Local Anaesthesia in Craniotomies**

   The history of neuroanaesthesia probably dates back to 8000 BC as evidenced by discovery of ancient trephined skulls belonging to the Neolithic period, although it is uncertain whether trephination was part of a surgical procedure or a religious ritual. The earliest written record of neurosurgery is found in Edwin Smith papyrus, which was, perhaps, written by Imhotep in Egypt between 3000 and 2500 BC.
This papyrus enumerates 48 case reports of injuries to the head, neck and vertebral column along with descriptions of surgeries on various parts of the body. Trephined skulls dating to 500 BC were discovered in Peru where the surgical holes were covered with cotton dressings, implying that brain surgery was being performed in South America as early as 500 BC.

It is presumed that anaesthesia in the prehistoric era was administered by locally applying a mixture of coca and yucca, which contained atropine, scopolamine and hyoscyamine. Greeks and Romans used datura, hyoscyamine and opium topically and alcohol for its hypnotic action. They also applied pressure on the carotid artery (“artery of sleep”) to induce unconsciousness. In the middle ages, sponges soaked in water hemlock, opium and ivy were applied to the nose to induce sleep.

The latter half of the nineteenth century marks the modern era of neuroanaesthesia when diethyl ether and chloroform were first used in neurosurgical interventions. Chloroform was popular in Britain in view of its ability to lower blood pressure and secondarily bleeding. A lower incidence of headache and excitement were noted with chloroform when compared with ether.

On the other hand, ether was preferred in the United States in view of its ability to maintain blood pressure and respiration. William Macewen, who was the first neurosurgeon who excised a meningioma under endotracheal intubation, suggested the necessity of tracheal intubation for neurosurgical procedures. Harvey Cushing, the founder of neurosurgery, was the first to maintain an anaesthesia record (“ether record”) wherein he recorded pulse rate, respiration, temperature and, later, blood pressure. He emphasised the importance of maintaining blood pressure, pulse rate and artificial ventilation during neurosurgical procedures.
After World War II, three groups promoted advances in the field of neuroanaesthesia namely, Glasgow Group, Pennsylvania Group and Mayo Clinic. Dr. Michenfelder of Mayo Clinic is believed to have coined the term “neuroanaesthesia”\textsuperscript{5}.

The first double-blind randomized study to compare the effects of 0.5% bupivacaine and saline when injected along the line of reflection of the scalp flap was performed by Hillman et al in the middle 1980’s\textsuperscript{6}. Four years later Hartley et al demonstrated cardiovascular stability in children undergoing supratentorial craniotomy in whom bupivacaine with epinephrine was injected along the line of incision and scalp reflection\textsuperscript{7}. However, both Hillman and Hartley used only scalp infiltration and not scalp nerve block in their respective endeavours.

Girvin was the first to describe the scalp block technique in awake craniotomy in 1986\textsuperscript{8}. It was not until 1992, however, when scalp block technique became popular after Rubial et al demonstrated that blocking the nerves of the scalp with mepivacaine was superior to local infiltration of the scalp with the local anaesthetic as well as intravenous fentanyl in maintaining cardiovascular hemodynamic stability during craniotomy\textsuperscript{9}. Subsequently, several studies were carried out in patients undergoing supratentorial craniotomy that proved the superiority of combining regional anaesthetic technique with general anaesthesia in patients undergoing craniotomy as enumerated in the section on “scalp nerve block”.

3. **Anaesthetic Concerns in Supratentorial Craniotomies**

The cornerstone of neuroanaesthesia is the prudent manipulation of the intracranial pressure-volume relationship. The main normal intracranial components of the brain (tissue, blood and cerebrospinal fluid) are contained in an unyielding
skull. The primary goal of neuroanaesthesia is to avoid intracranial compartment volume increase, especially for cerebral blood volume, by judicious choice of anaesthetic agents and their optimal dosages, maintaining mean arterial pressure to preserve cerebral autoregulation and optimising partial pressure of carbon dioxide in the blood.

Close hemodynamic monitoring warrants placement of an invasive arterial line for beat-to-beat monitoring of blood pressure; risk of bleeding and venous air embolism, need to infuse vasoactive drugs and evidence of cardiovascular compromise indicate the need for central venous catheter placement; in addition to pulse oximetry, electrocardiogram and end tidal carbon dioxide, the need for special monitoring is decided on a case-to-case basis: neuromuscular monitoring should be used if myorelaxants are given during the surgery, electroencephalography (EEG) monitoring can inform the anaesthesiologist about cerebral ischemia and depth of anaesthesia; monitoring of evoked potentials is helpful in observing intactness of specific central nervous system pathways during surgical manipulation.

Anaesthetic aims during maintenance of anaesthesia during supratentorial surgery are:

i) Control of brain tension via control of cerebral blood flow and cerebral metabolic rate (chemical brain retractor concept). Components of this concept encompass the following:

- Mild hyperosmolality (use 0.9% saline) as baseline infusion; give 20% mannitol 0.5 – 0.75 gm/kg before bone flap removal.
- Intravenous anaesthetic agent (propofol) to provide adequate depth of anaesthesia
- Mild hyperventilation
- Mild controlled hypertension: mean arterial blood pressure of 100mmHg to decrease cerebral blood volume and intracranial pressure
- Normovolemia
- Mild hyperoxia
- Head up positioning, no compression of jugular veins
- Minimal positive end-expiratory pressure
- Avoid bucking on ventilator by using adequate muscle relaxant
- Avoid brain retractor
- Lumbar drainage

ii) Neuroprotection through maintenance of optimal intracranial environment: maintain a good match between cerebral substrate demand and supply. Although some anaesthesiologists use modest hypothermia (35° degrees Celsius) to provide neuroprotection although clinical studies have not demonstrated any beneficial effect of the same in neurosurgical patients\textsuperscript{10}.

Awakening from neurosurgery mandates maintenance of stable arterial blood pressure (and thus, cerebral blood flow and intracranial pressure), stable oxygenation and carbon dioxide tension and normothermia as well as avoidance of coughing and raised airway pressure.
4. Postoperative Pain Management in Supratentorial Craniotomies: Modalities and Challenges

Analgesia in postoperative neurosurgical patients presents a unique challenge: on one hand, inadequate analgesia may cause agitation, hypertension and vomiting, which increase the risk of intracranial bleed; on the other hand, narcotic analgesics may cause respiratory depression and hypercapnia, which result in cerebral vasodilatation and increased intracranial pressure.

Pain experienced by patients after craniotomy seems to be of somatic origin, most likely involving the scalp, pericranial muscles and soft tissue, and from manipulation of duramater. De Benedittis et al undertook a pilot study to assess prevalence of pain in postoperative craniotomy patients and quoted a figure of 60% for moderate to severe pain.\(^1\)

Among craniotomies, supratentorial surgeries are considered to be less painful than infratentorial procedures.\(^2\) There is evidence that pain after neurosurgical procedures is more severe than expected, resulting in inadequate treatment of pain by the perioperative team.\(^3\) Although pain may often be treated as a secondary concern, uncontrolled pain has systemic side effects that may directly affect patient outcome. Systemic organ responses to pain are enumerated below in table 1.\(^4\)
Table 1: Systemic organ responses to pain:

| Respiratory | Increased skeletal muscle tension  
<table>
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<th>Decreased total lung compliance</th>
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| Endocrine   | Increased adrenocorticotropic hormone, cortisol, glucagon, epinephrine, aldosterone, antidiuretic hormone, catecholamines and angiotensin II  
|             | Decreases in insulin and testosterone |
| Cardiovascular | Increased myocardial work (mediated by catecholamines, angiotensin II) |
| Immunologic | Lymphopenia  
|             | Depression of reticuloendothelial system  
|             | Leukocytosis  
|             | Reduced killer T-cell cytotoxicity |
| Hematologic | Increased platelet adhesiveness  
|             | Diminished fibrinolysis  
|             | Activation of coagulation cascade |
| Gastrointestinal | Increased sphincter tone  
|             | Decreased smooth muscle tone |
| Genitourinary | Increased sphincter tone  
|             | Decreased smooth muscle tone |
In general, short-acting analgesics are preferred because they allow interruption for neurologic examination. To avoid peaks and troughs with the use of short-acting agents, administration by continuous infusion is preferred. Commonly used drugs include fentanyl, remifentanil and dexmedetomidine\textsuperscript{15}.

Opioids are commonly used for postoperative analgesia. They exert their effects by stimulating the mu (analgesia), sigma and kappa subtypes of opioid receptors, which are widely distributed in the central and peripheral nervous systems. Codeine, oxycodone, hydrocodone, propoxyphene, and morphine have traditionally been used in the treatment of post-craniotomy pain in neurosurgical patients\textsuperscript{16,17}.

The use of opioids bears the risk of delayed recovery and ambulation, respiratory depression, nausea, vomiting, constipation and pruritus, greater length of hospital stay, and a higher risk of neurologic complications. Intramuscular codeine is preferred over morphine in view of the fact that it is associated with lesser respiratory depression compared to morphine and does not affect pupil size.

Morad et al in their study concluded that patient controlled analgesia (PCA) with fentanyl was superior to an as needed dose (prn) of fentanyl and that there was no increase in side effects of opioids in the PCA arm although the dose of fentanyl used in the PCA arm was almost twice that of the prn arm\textsuperscript{18}. It is worthy of note that this study was carried out in an intensive care unit staffed for 24 hours with neuro-intensivists and highly trained nurses. Hence, the results drawn from the study may not be replicable in places with lesser resources.

Nonsteroidal anti-inflammatory drugs (NSAID’s) are excellent alternatives to opioids in providing analgesia to craniotomy patients. They exert their analgesic effects by inhibiting the cyclooxygenase (COX) enzyme, which has two isomers: COX1 and COX2. The COX 2 isomer is responsible for analgesia whereas the propensity to cause platelet dysfunction and,
hence, prolonged bleeding time is attributed to the COX 1 isomer. The administration of perioperative NSAID’s has been described as a major risk factor for postoperative bleeding\textsuperscript{19}, particularly after hematoma evacuation, aneurysm repair and resection of arterial venous malformations.

As cyclooxygenase 2 (COX-2) inhibitors are not associated with an increased risk of bleeding after craniotomy\textsuperscript{20}, there is a growing interest in considering their role in the postoperative analgesic armamentarium. Jones et al studied the effect of parecoxib on analgesia after craniotomy and found that it reduced pain scores after 6 hours as well as decreased morphine requirement at 8 and 12 hours postoperatively\textsuperscript{21}. However, it had no overall impact on postoperative analgesia in craniotomy patients as concluded in this trial.

In a study involving 96 patients, Williams DL et al found no benefit in adding intravenous parecoxib, a COX-2 inhibitor, to adult patients undergoing supratentorial craniotomy under propofol/remifentanil anaesthesia with local anaesthetic scalp infiltration, intravenous (IV) paracetamol and nurse-administered morphine in the post-anaesthesia care unit\textsuperscript{22}.

Nair S and Rajshekhar V studied post-operative pain intensity while using oral paracetamol as the sole analgesic in 43 patients who underwent supratentorial craniotomy under general anaesthesia\textsuperscript{23}. They noted that 63\% of patients complained of significant pain (Visual Analogue Scale score >3) during the 48 hour period of postoperative observation while only 12\% complained of severe pain within the first 12 hours. Maximum pain was noted at 8 hours postoperatively. After 12 hours, the pain scores showed a steady decline at 24 and 48 hours.

Tramadol is a relatively new analgesic that has been used for postoperative pain management for obstetric, orthopaedic and cardiothoracic procedure\textsuperscript{24}. It is believed to exert its analgesic effects by inhibiting the reuptake of serotonin and norepinephrine. As it has no effect on platelet function or coagulation, it is considered safe in neurosurgical patients.
In a randomized prospective study by Rahimi et al, 50 post-craniotomy patients were allocated to receive either narcotic with acetaminophen or narcotic with tramadol for postoperative pain relief (25 patients in each group)\textsuperscript{25}. The narcotic with acetaminophen group was noted to have higher pain scores, longer length of hospital stay and higher dose of narcotic used compared to the narcotic with tramadol group, thus, suggesting that addition of tramadol to narcotics for postoperative pain relief may provide superior analgesia, decrease the side effects of the narcotic agent, encourage earlier postoperative ambulation and diminish hospitalization costs.

Scalp infiltration with local anaesthetics has been evaluated with respect to its role in decreasing post-craniotomy analgesic requirement. As local anaesthetic infiltration lacks the systemic adverse effects of opioids, it would be a preferred mode of analgesia in neurosurgical patients. In 1998, Bloomfield et al studied intraoperative hemodynamics and postoperative pain scores in 43 patients who were randomly assigned to receive scalp infiltration with either 0.25% bupivacaine with adrenaline (1 in 200,000) or saline with adrenaline (1 in 200,000)\textsuperscript{26}.

Lower heart rate and mean arterial pressure (MAP) were recorded during skeletal fixation, skin incision and wound closure in the bupivacaine group in addition to lower pain scores in the first hour postoperatively. However, higher heart rate and MAP were noted in the first postop hour in the bupivacaine group despite the lower pain score. The intraoperative hemodynamic stability could be attributed to the sufentanil-based anaesthetic technique. However, as bupivacaine failed to blunt the postoperative rise in heart rate and MAP, it was concluded that post-craniotomy pain was not the primary determinant of postoperative hemodynamic activation.
In a prospective double-blinded randomized, placebo-controlled trial by Biswas BK et al in 2003 involving 41 patients, the 20 patients who received pre-incision scalp infiltration with 0.25% bupivacaine showed no difference in analgesic requirement at different time-intervals over a 48 hour postoperative period compared to the 21 patients in the placebo group who received normal saline in the scalp infiltration. However, fewer patients in the bupivacaine group required the first dose of rescue analgesic in the first post-op hour as compared to the placebo group (p value 0.61 and 0.44 respectively), suggesting that scalp infiltration with bupivacaine may delay the first analgesic dose.

The role of scalp nerve block in intra-operative and postoperative pain management is discussed subsequently.

**Scalp Nerve Blocks: Anatomy, Technique, Complications, Efficacy**

**Anatomy:**

The pain sensitive structures in the central nervous system include skin, pericranial muscles, periosteum of skull bone and duramater. Sensory innervation of the scalp and forehead is provided by the trigeminal and spinal nerves. There are six branches of the aforementioned nerves that need to be blocked bilaterally to provide anaesthesia to the scalp: the forehead and anterior scalp are supplied by the supraorbital and supratrochlear nerves, with temporal sensory innervation by zygomaticotemporal and auriculotemporal nerves; the posterior aspect of the scalp is innervated by the greater occipital nerve and the skin behind the ear by the lesser occipital nerve.
There may be minor contributions from the greater auricular nerve and third occipital nerve; however, these rarely encroach on the surgical field. It is imperative to ascertain the depth of needle insertion required to deposit the local anaesthetic in the correct layer of the scalp to maximise efficacy of the block. A brief description of the location of each nerve is included in the following paragraphs:

1. Supraorbital Nerve: is located just above the supraorbital notch and local anaesthetic is injected just superficial to the periosteum.
2. Supratrochlear Nerve: is situated medial the supraorbital nerve in the same plane described above.
3. Temporal branch of the Auriculotemporal Nerve: is located immediately posterior to the superficial temporal artery at the level of the external auditory meatus. The local anaesthetic must be injected superficially and subcutaneously as too deep an injection may paralyse the facial nerve.
4. Zygomaticotemporal Nerve: emerges from the temporalis fascia at the lateral border of the orbit with many small deep branches ramifying within the temporalis muscle. It is important to block these small branches in temporally based flap incisions. Field infiltration above the zygoma through the temporalis muscle and down to the periosteum of the temporal bone will provide an adequate block without causing facial nerve paralysis.
5. Lesser Occipital Nerve: is blocked at the upper, posterior border of the sternocleidomastoid muscle either deep or superficial to the fascia.
6. Greater Occipital Nerve: is blocked by subcutaneous infiltration of local anaesthetic along the middle third of a line joining the mastoid process to the external occipital protuberance along the superior nuchal ridge. This injection will also reinforce the lesser occipital nerve block as it becomes subcutaneous.
**Technique:**

No specific type of needle is prescribed in performing the scalp block. 1-2 ml of local anaesthetic mixed with adrenaline may be injected at each nerve site (up to 5 ml on the operative side at the zygomaticotemporal nerve) after ensuring that the toxic dose of the particular local anaesthetic for the patient’s body weight has not been exceeded.

Figure 1: Innervation of the scalp and face. Source: Lalwani AK: Current Diagnosis &Treatment in Otolaryngology - Head and Neck Surgery, 2nd edition: (www.accessmedicine.com)
Local anaesthetics used in scalp nerve blocks:

Lignocaine, bupivacaine and ropivacaine are most often used in performing scalp nerve blocks. They are classified as amides based on the nature of their carbonyl-containing linkage group. They exert their clinical effects by blockage of sodium channels, thereby, preventing sodium ion flux across the cell membrane, resulting in reversible interruption of nerve impulses in peripheral nerves\textsuperscript{30}. They are metabolised primarily by the cytochrome P450 enzymes in the liver by N-dealkylation and hydroxylation.

Their rate of metabolism is as follows: lignocaine > ropivacaine > bupivacaine. Less than 5% of their unchanged form is excreted by the kidneys. Anaesthetic potency of the local anaesthetic depends on lipid solubility, while onset of action is determined by pKa (the pH at which there is equal concentration of local anaesthetic in the ionized and non-ionized forms), dose of local anaesthetic administered and the concentration used.

Table 2: pKa of local anaesthetics used in scalp block

<table>
<thead>
<tr>
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<tr>
<td>Lignocaine</td>
<td>7.8</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>8.1</td>
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Duration of action of these local anaesthetics is determined by their protein binding, concentration used, time of contact with tissue and type of vascular bed\textsuperscript{31}. The extent of systemic absorption depends on site of injection (intravenous > tracheal > intercostals > caudal > paracervical > epidural > brachial > sciatic > subcutaneous), dose injected, addition of a vasoconstrictor and pharmacological profile of the local anaesthetic. Ropivacaine is the (s)-enantiomer of 1-propyl-2’, 6’- piperidoxylidide, closely resembling the structures of mepivacaine and bupivacaine as shown below.

**Figure 2: Structure of Bupivacaine and Ropivacaine**
**Efficacy:**

In 1996, Pinosky et al was the first to demonstrate effective attenuation of the hemodynamic response to cranial pin application when scalp nerve block was performed with 0.5% bupivacaine 5 minutes prior to pinning\(^3^2\).

In 2005, Yildiz et al compared the suppression of hemodynamic response to cranial pins with intravenous fentanyl bolus versus an intravenous bolus of fentanyl given in conjunction with a scalp nerve block. Although there seemed to be no significant difference between the two groups, this study did not explore the possibility of delayed emergence with opioid bolus or the postoperative analgesic role of scalp nerve block\(^3^3\).

Nguyen et al studied 30 cases of supratentorial craniotomy which were randomly allocated to receive either 0.75% ropivacaine or saline in the scalp nerve block at the conclusion of the surgery and prior to extubation\(^3^4\). Although the average visual analogue scale (VAS) scores were higher in the saline group as compared with the ropivacaine group over a 48 hour period (3.7±2.4 versus 2.0±1.6, p value 0.036), the two groups did not differ with respect to the total dose of subcutaneous codeine administered for postoperative pain relief or the time duration prior to first dose of postoperative analgesic.

In a pilot study by Gazoni et al in 2008\(^3^5\), 30 patients with supratentorial tumours were enrolled into one of 2 groups: one group of 14 patients receive a scalp block with 0.5% ropivacaine prior to cranial pin application and another group of 16 patients who did not. Although the scalp nerve block group showed lesser hemodynamic response to pin application, there was no difference between the two groups with respect to concentration of volatile agent and dose of remifentanil used intra-operatively, post-operative pain scores, amount of narcotic required for post-operative analgesia and incidence of nausea and vomiting.
More recently, in a study of sixty patients undergoing elective craniotomy, Tuchinda et al randomized them into three groups: group A received 0.5% bupivacaine with adrenaline in the scalp nerve block, group B received 0.25% bupivacaine with adrenaline in the scalp nerve block and group C received saline with adrenaline in the skull block\textsuperscript{36}. There were higher mean arterial pressure readings noted in group C during cranial pin insertion and skin incision as well as higher requirement of fentanyl intra-operatively compared to group A and B. However, there was no significant difference between the three groups with respect to time of first dose of post-operative rescue analgesic, pain scores and total dose of postoperative morphine consumption. This study seems to imply that scalp nerve block plays a role only in attenuating hemodynamic response to noxious surgical stimuli intra-operatively and has no significant role in post-operative analgesia.

**Complications:**

Although uncommon, complications owing to scalp blocks have been reported. The addition of a vasoconstrictor to the local anaesthetic drug used for the scalp block poses a risk of inadvertent intravascular injection or systemic absorption, which could result in hypertension\textsuperscript{37}. There is also the possibility of systemic absorption of a large volume of local anaesthetic during a scalp block, given the immense vascularity of the scalp. This may predispose to local anaesthetic toxicity\textsuperscript{38}.

The proximity of the facial nerve to the auriculotemporal nerve makes facial nerve paralysis a potential complication of a scalp block. As with any procedure, infection remains a possibility after a scalp nerve block, especially in view of the multiple sites of needle entry while giving the block. If a scalp nerve block is administered to a patient with coagulopathy (this is a relative contraindication for a scalp block), it would result in profuse bleeding and hematoma formation.
6. Dexamethasone: a novel adjuvant in peripheral nerve blocks

Dexamethasone is a long acting synthetic glucocorticoid which is twenty five times more potent than cortisol in its glucocorticoid activity but has minimal mineralocorticoid activity. Unbound dexamethasone crosses cell membranes and binds tenaciously to specific cytoplasmic receptors. This complex of dexamethasone with the receptor binds to DNA (deoxyribonucleic acid) elements called glucocorticoid response elements resulting in a modification of transcription, which alters protein synthesis in order to achieve inhibition of leukocyte infiltration at the site of inflammation, interference in the mediators of inflammatory response, suppression of humoral immune responses and reduction in scar tissue.

The anti-inflammatory actions of dexamethasone are believed to involve phospholipase A2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes. The mechanism of action whereby dexamethasone affords anti-emetic activity is unknown. Molecular formula of dexamethasone is C_{22}H_{29}FO_{5} and its molecular weight is 392.47. It is designated chemically as 9-fluoro-11β, 17, 21 – trihydroxy - 16α – methylpregna – 1, 4 – diene, 3, 20 – dione.

**Figure 3: Chemical structure of dexamethasone**
Dexamethasone is 70% protein-bound and has an elimination half-life of 1.8 – 3.5 hours in persons with normal renal function. Its biological half-life is 36 – 54 hours. It is primarily metabolised in the liver and excreted in urine and faeces. The proportion of glucocorticoid to mineralocorticoid activity of dexamethasone in comparison with other corticosteroids is summarised in the following table.

Table 3: Table comparing glucocorticoid and mineralocorticoid activity of various corticosteroids

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Glucocorticoid activity</th>
<th>Mineralocorticoid activity</th>
<th>Equivalent oral or intravenous dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0.8</td>
<td>25</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>0.75</td>
</tr>
</tbody>
</table>
As noted from the tabulation above, dexamethasone is one of the corticosteroids with the highest glucocorticoid activity and least mineralocorticoid activity.

Adverse effects associated with the use of dexamethasone include cardiovascular (bradycardia, cardiac arrest, cardiomyopathy, heart failure, circulatory collapse, edema, hypertension, myocardial rupture following myocardial infarction, syncope, thromboembolism, vasculitis), central nervous system (depression, emotional instability, euphoria, headache, intracranial pressure increased, insomnia, malaise, mood swings, neuritis, personality changes, pseudo tumor cerebri, seizure, vertigo), dermatologic (acne, allergic dermatitis, alopecia, angioedema, bruising, dry skin, erythema, fragile skin, hirsutism, hyper-/hypopigmentation, hypertrichosis, perianal pruritus, petechiae, rash, skin atrophy, skin test reaction impaired, striae, urticaria, impaired wound healing), endocrine and metabolic (adrenal suppression, carbohydrate tolerance decreased, Cushing's syndrome, diabetes mellitus, glucose intolerance decreased, growth suppression in children), hyperglycemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary-adrenal axis suppression, protein catabolism, sodium retention), gastrointestinal (abdominal distension, increased appetite, gastrointestinal haemorrhage, gastrointestinal perforation, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain), genitourinary (increased or decreased spermatogenesis), hepatic (hepatomegaly, elevated transaminases), local (post-injection flare following intra-articular use, thrombophlebitis), neuromuscular and skeletal (arthropathy, aseptic necrosis of femoral and humoral heads, fractures, loss of muscle mass, myopathy particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents, neuropathy, osteoporosis, paraesthesia, tendon rupture, vertebral compression fractures, weakness), ocular (cataracts, exophthalmos, glaucoma), renal (glycosuria), respiratory (pulmonary edema), miscellaneous (abnormal fat
deposition, anaphylactoid reaction, anaphylaxis, diaphoresis, hiccups, hypersensitivity, impaired wound healing, infections, Kaposi's sarcoma, moon face, secondary malignancy).

Contraindications to the use of dexamethasone include anaphylaxis to the drug per se or to a component of its formulation, systemic fungal infection and cerebral malaria.

Uses of dexamethasone in clinical practice range from anti-inflammatory to immunosuppressant agent, used in the treatment of a host of disorders including allergic conditions (asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, allergic rhinitis and serum sickness), dermatologic disease (bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, and Stevens-Johnson syndrome), gastrointestinal diseases (ulcerative colitis), hematologic conditions (autoimmune haemolytic anemia, congenital hypoplastic anemia, idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia), neoplastic diseases (palliative management of leukemias and lymphomas), disorders involving the nervous system (acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumour or head injury), ophthalmic diseases (sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids), renal diseases (to induce a diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus), respiratory diseases (berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis) and rheumatic disorders (acute gouty arthritis, acute rheumatic carditis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis, dermatomyositis, polymyositis, and systemic lupus erythematosus).
Specific uses of dexamethasone in anaesthetic practice include prevention of post-operative nausea and vomiting\(^{39}\), perioperative management of cerebral edema, reduction of airway edema\(^{40}\) and post-operative pain in tonsillectomy and dental surgery\(^{41,42}\).

The use of dexamethasone as an adjuvant to anaesthetics can be considered under two headings: adjuvant to general anaesthetics and adjuvant to regional blocks. When given intravenously during the course of general anaesthesia, dexamethasone reduces pain from tonsillectomy in adults (10 mg) and dental surgery (4 – 16 mg) as mentioned earlier. It is more effective as an analgesic when given in conjunction with a non-steroidal anti-inflammatory drug in patients undergoing tonsillectomy\(^{43}\). Four mg of dexamethasone administered to patients undergoing anorectal procedures hastened to the time to discharge without a concurrent increase in wound-related complications\(^{44}\). However, it provided no analgesic benefit in patients undergoing gynecologic procedures or mastoidectomy\(^{45,46}\).

The role of dexamethasone as an adjuvant in regional blocks is considered in the following paragraphs.

Kopacz et al showed that dexamethasone in a biodegradable microcapsule form with bupivacaine prolonged the duration of intercostal nerve blockade in healthy human volunteers\(^{47}\). Dexamethasone was used as an adjuvant in a double-blinded prospective randomized control study by Movafegh et al in 2006\(^{48}\) in sixty patients undergoing forearm and hand surgery under axillary block. They were divided into two groups: one group received 1.5% lignocaine with 2 ml of saline and the other received 1.5% lignocaine and 2 ml (8 mg) of dexamethasone in the axillary block. There was no significant difference in the onset of sensory and motor blockade in both groups. However, the duration of sensory and motor blockade was significantly prolonged in the dexamethasone group.
Cummings III et al published a study in the British Journal of Anaesthesia in 2011 on the role of dexamethasone as an adjuvant to ropivacaine and bupivacaine in interscalene blocks\textsuperscript{49}. This study showed that dexamethasone significantly prolongs the duration of analgesia afforded by both ropivacaine and bupivacaine, more so with ropivacaine. The median maximum Verbal Response Scores for pain were significantly lower in the dexamethasone with ropivacaine and dexamethasone with bupivacaine groups compared to the groups receiving plain ropivacaine and plain bupivacaine on the first post-operative day.

Several other studies have deduced that dexamethasone added to the local anaesthetic drug prolongs the duration of analgesia afforded by interscalene blocks\textsuperscript{50,51}. However, literature on the use of steroids as adjuvants in scalp nerve block is scarce.

In a letter to the editor in the Korean Journal of Anaesthesiology in August 2011, Hee-Soo Kim et al, 39 children with Moyamoya disease, who were scheduled to undergo encephaloduroarteriosynangiosis under general anaesthesia, were divided randomly into two groups: one group received ropivacaine with epinephrine in the scalp block while the other received ropivacaine with triamcinolone (a steroid). There was no improvement in the quality of the block or duration of postoperative analgesia in the two groups, leading the authors to conclude that addition of triamcinolone to the local anaesthetic in the scalp block does not yield any advantage over use of the plain local anaesthetic in this subset of patients\textsuperscript{52}.

There is no literature on the use of dexamethasone as an adjuvant to local anaesthetic agents used in scalp nerve block.
The mechanism whereby dexamethasone is purported to exert its action as an adjuvant in nerve blocks is twofold:

a) Corticosteroids are known to cause vasoconstriction on topical application, which is mediated by the occupancy of classic glucocorticoid receptors$^{53,54}$. According to this theory, steroids bind to intracellular receptors and modulate nuclear transcription.

b) The other proposition is that steroids exert their analgesic property via systemic effects$^{55}$.

A feared complication of adding dexamethasone perineurally is nerve injury, although this is rare and is more likely related to needle trauma than the dexamethasone injection$^{56}$. Serious systemic side effects of dexamethasone include hyperglycaemia, especially in diabetic patients, compromised immunity, myocardial dysfunction, poor wound healing, reactivation of latent tuberculosis, peptic ulcer and gastrointestinal bleed.

7. **Pre-operative Pain Assessment : Methods, Role in Predicting Post-operative Analgesic Requirement**

Various techniques have been attempted to predict post-operative pain by assessment of pre-operative pain threshold:

(a) In 2003, Granot et al studied the role of preoperative pain assessment using heat pain threshold and magnitude estimation of supra-threshold pain in 58 women scheduled for elective Caesarean section$^{57}$. They estimated the heat pain threshold by applying a thermode on the volar aspect of the hand and gradually increasing the temperature from 32 degrees Celsius at a rate of 1 degree Celsius per second, allowing an inter-stimulus interval of 5 seconds. The patient would indicate the point
at which the painless warm sensation became a painful heat sensation. They estimated the magnitude of supra-threshold noxious stimulation by applying phasic heat stimuli at five different temperatures (44, 45, 46, 47 and 48 degree Celsius) and asking the women to express the intensity of pain and unpleasantness experienced using a 100 point Visual Analogue Scale (0 would mean no pain and 100 would imply worst imaginable pain). In this study, heat pain threshold did not correlate with post-operative pain while preoperative pain scores with supra-threshold pain stimulus at 48 degree Celsius correlated best with post-Caesarean pain scores.

(b) Pan et al studied multiple pre-operative variables as predictors for post-Caesarean section pain in 34 healthy parturients\textsuperscript{58}. The following parameters were assessed pre-operatively: thermal pain threshold, intensity, and unpleasantness to heat stimuli applied to arm and lower back, State Trait Anxiety Inventory, and patient expectation for postoperative pain and need for analgesia. Post-operatively, resting pain, movement pain and analgesic consumption were recorded.

Their results were as follows: resting pain was predicted by thermal pain and unpleasantness as well as patient expectation; evoked pain was predicted by thermal pain threshold in the back; composite pain was predicted by thermal pain and unpleasantness and pre-operative blood pressure; intra-operative analgesic requirement was predicted by pre-existing pain; recovery room analgesia by thermal pain threshold and State Trait Anxiety Inventory; total analgesic need by State Trait Anxiety Inventory.
(c) Werner et al induced a burn injury using a contact thermode (12.5 cm², 47°C for 7 minutes) and assessed the pain threshold of 20 patients posted for arthroscopic knee surgery and compared this with post-operative Visual Analogue Scale scores during limb movement. They found a good correlation between the preoperative and post-operative pain scores⁵⁹.

(d) Yung-Wei Hsu et al assessed pre-operative pressure pain threshold in forty women undergoing lower abdominal gynaecological surgery⁶⁰. They applied an electronic pressure algometer probe with a surface area of contact of 1 cm² on the third finger of the right hand. They increased the pressure applied by the probe by 30 kPa/second until the patient first indicated that she had pain. This was taken as the patient’s pre-operative pain threshold. The pressure at which the patient indicated she could not bear the pain any more was taken as the pain tolerance threshold. The pain tolerance was found to correlate with the post-operative Visual Analogue Scale and with morphine consumption in the first 24 hours after surgery.

(e) Slappendel et al evaluated the correlation between pre-operative Visual Analogue Scale (VAS) scores with post-operative pain scores and morphine consumption in sixty patients undergoing total hip replacement under spinal anaesthesia⁶¹. It was found that only in patients who experienced severe pre-operative pain (defined as VAS 7-10) did the pre-operative VAS score correlate with higher post-operative morphine consumption.
(f) In a review article in Anaesthesiology in February, 2011, fifteen studies were reviewed wherein pre-operative pain sensitivity was compared with post-operative pain intensity to look for a correlation between the two. In these studies, 3 types of pain stimuli were applied namely thermal, pressure and electrical pain. It was deduced that suprathreshold heat pain (pain beyond the patient’s threshold) correlated consistently with post-operative pain while other pain variables showed inconsistent results with respect to correlation with post-operative pain outcomes.

(g) Rago et al evaluated the role of pre-operative Visual Analogue Scale (VAS) in response to inflation of a sphygmomanometer cuff to 250 mmHg for five minutes in predicting post-operative pain threshold and post-operative analgesic requirement. They divided 32 patients scheduled to undergo thyroidectomy into three groups based on pre-operative pain tolerance (VAS <3, VAS 3-6 and VAS >6) and found that patients with lower pre-operative VAS scores required less post-operative analgesic medication compared to those who had a higher pre-operative VAS score.

We too applied this tourniquet test in assessing pre-operative VAS score in our patients undergoing supratentorial craniotomy under general anaesthesia because it is safe, simple, reproducible, accurate and inexpensive.
MATERIALS AND METHODS
Patient Selection and Methodology:

Settings:

This study was carried out in the three neurosurgery operating theatres and neurosurgery intensive care unit of Christian Medical College and Hospital, Vellore, which is a two thousand bedded tertiary care hospital that caters to 90,000 in-patients and 1.5 million outpatients annually. The twelve bedded neuro intensive care unit, four bedded neurotrauma ICU and ten bedded neuro high dependency unit (HDU) cater to the needs of pre-operative, post-operative and neurotrauma patients. Given the tremendous load of patients who need intensive care, these ICU’s are equipped with state-of-the-art ventilators and monitors to adapt to the special needs of those who are critically ill. About 400 to 500 craniotomies are performed each year in our institution, of which more than 70% are supratentorial craniotomies.

Patient Selection:

Inclusion Criteria:

1. Adult patients (age more than 18 years) diagnosed with intracranial space-occupying lesions scheduled for elective supratentorial craniotomy
2. ASA I to III
3. Pre-operative GCS 15/15

Exclusion Criteria:

1. Patients who have undergone previous craniotomy
2. Hypertensive patients on beta blockers
3. Patients diagnosed with diabetes mellitus
4. Pre-operative Glasgow Coma Scale (GCS) less than 15
5. Pregnant patients
6. Patients with known allergy to local anaesthetics
7. Patients with peptic ulcer disease
8. Patients with coagulopathy
9. Patients with scalp infection
10. Patients who refused to give consent to participate in the study

**Methodology:**

The study recruited 90 consecutive patients who fulfilled the inclusion criteria between March 2012 and September 2012 after informed consent was obtained. The study protocol received approval from the Institutional Review Board and Ethics Committee of the Christian Medical College, Vellore, and was funded by the fluid research grant of the Christian Medical College.

All patients were educated regarding the ten point Visual Analogue Scale (VAS) score the day prior to scheduled surgery. A score of zero indicated ‘no pain’ while a score of ten implied ‘worst imaginable pain’. A pre-op VAS score was determined for each patient recruited into the study using a sphygmomanometer inflated to 250 mmHg for 5 minutes, with patients asked to quantify the pain of the inflated cuff. On the day of surgery, patients were premedicated with oral diazepam and metoclopramide and wheeled into the operating theatre.
Pulse oximetry, three lead electrocardiogram, arterial invasive blood pressure were monitored from the time of pre-oxygenation and induction and end tidal carbon dioxide, nasal or oral temperature, urine output, neuromuscular monitoring and blood sugar levels were monitored after induction. A peripheral line, central line (brachial central venous line or subclavian central venous line) and radial arterial line were inserted for all patients. They were induced with 5 mg/kg thiopentone or 2 mg/kg propofol, 1-2 mcg/kg fentanyl and 0.15 mg/kg vecuronium.

After oral intubation with cuffed endotracheal tube, anaesthesia was maintained with isoflurane 0.8 – 0.9 minimum alveolar concentration (MAC), oxygen and air, muscle relaxation with an infusion of vecuronium titrated to maintain two out of four twitches on train of four on the neuromuscular monitor. The dose of fentanyl was titrated to obtund heart rate and blood pressure response to surgical stimulation, with a maximum dose of 4 mcg/kg. Any further heart rate or blood pressure rise in response to surgical stimulation was treated with intravenous propofol boluses of 1 mg/kg each time.

After induction of general anaesthesia, a scalp nerve block was performed. The toxic dose of lignocaine (7mg/kg with 5 mcg/cc adrenaline) and ropivacaine (3mg/kg) for the patient’s body weight were calculated to ensure that this was not exceeded. 10 ml of 2% lignocaine and 30 ml of 0.2% ropivacaine were mixed in a bowl. 20 micrograms of adrenaline were added to this mixture to make the concentration 5 mcg/cc of adrenaline in the 40 ml of local anaesthetic mixture. The study drug was added to this local anaesthetic and adrenaline mixture.
In keeping with the double blinded nature of the study, permuted block randomization sequence using SAS 9.1.2 software was employed to calculate the randomization sequence. The randomization sequence was enclosed in opaque sealed envelopes and sent to the hospital pharmacy, where the study drugs were prepared and enclosed in amber coloured serially numbered vials. For each serially numbered vial with the study drug, there was a corresponding serially numbered opaque envelope which contained the Group to which the patient was to be recruited in the study: either Group 1 or Group 2.

The study drug may be either 2 ml of saline or 2 ml of 8 mg dexamethasone. The envelope was opened by the concerned anaesthesiologist just prior to administration of the scalp nerve block. The serial number on the envelope was noted to correspond with the serial number on the study drug vial. Which Group (1 or 2) contained which study drug (saline or dexamethasone) was unknown to the anaesthesiologist performing the block as well as to the principal investigator, in keeping with the double blinded nature of the study.

Using aseptic technique, the scalp was cleaned with 2% v/v chlorhexidine gluconate skin prepping solution and the local anaesthetic, adrenaline and study drug mixture was administered at the following points:

1. Supraorbital nerve: local anaesthetic was injected superficial to the periosteum above the supraorbital notch.
2. Supratrochlear nerve: local anaesthetic was injected just medial to the supraorbital nerve.
3. Zygomaticotemporal nerve: local anaesthetic was injected at the lateral border of the orbit as well as field infiltration above the zygoma down to the periosteum of the temporalis bone.

4. Lesser Occipital nerve: local anaesthetic was injected at the upper posterior border of sternocleidomastoid muscle insertion.

5. Greater Occipital nerve: local anaesthetic was injected subcutaneously along the middle third of a line joining the mastoid process with the external occipital protuberance along the superior nuchal ridge.

The block was performed with a 22G Quincke spinal needle so that a ring block could be performed after the individual nerve points were anaesthetised bilaterally.

Intra-operatively, the pulse rate and blood pressure were noted at induction, 5 minutes after intubation, at insertion of cranial pins, skin incision, craniotomy and dura opening. If there was significant rise in heart rate or blood pressure during pin insertion or skin incision, the scalp nerve block was considered inadequate (“failed scalp nerve block”). Significant rise in heart was taken as an increase of 10 beats/minute from the baseline heart rate immediately prior to the stimulus; significant rise in blood pressure referred to a 10% elevation from the baseline mean arterial pressure (MAP) just prior to the stimulus. Any significant rise in heart rate and blood pressure during the tumour excision were also noted.

At the conclusion of the surgery, significant elevation in heart rate and MAP were noted at dural closure, closing of bone flap, skin suturing and removal of pins. The total dose of fentanyl and propofol used intra-operatively were noted. After removal of cranial pins, the volatile agent was discontinued without tapering, neostigmine was administered to reverse muscle relaxation and patient was extubated when awake or
able to protect his airway. The time from discontinuation of isoflurane and extubation was noted in both the groups.

All the patients who underwent supratentorial craniotomy were observed for at least 24 hours in the neuro ICU after surgery. The Glasgow Coma Scale (GCS) and VAS score for post-operative pain were noted by the ICU nurses at 1 hour, 4th hour, 8th hour, 12th hour and 24th hour post-operatively. If the GCS was less than 14, no VAS score was recorded. Any complications such as hyperglycaemia, post-operative nausea and vomiting, seizure, re-operation and post-operative ventilation were noted.

**Sample size:**

Kaplan Meier estimates were calculated to assess the mean time when the second complaints (i.e. second rescue analgesic was needed) were made in each of the two groups. Log rank test was planned to compare the time to the second complaint after the treatments were assigned. With regard to secondary outcomes, the VAS recorded in both the groups would be presented in both the groups in terms of mean and standard deviation. The dose requirement would be compared using the mean and standard deviations in both the groups. The proportion of nausea would also be compared between the two groups by calculating the proportions in each group.

The study was powered to detect whether dexamethasone added as adjuvant to 0.2% ropivacaine in the scalp nerve block was superior to plain ropivacaine with regard to the primary end point. Based on the study by Tuchinda et al who quoted a scalp block duration of 246 minutes (4.1 hours), we calculated using survival analysis that a sample of 81 patients in each group would provide 80% statistical power to detect a 33% relative increase in the time to first analgesic in the treatment group with two sided alpha error of 2%.
Table 4: Survival analysis comparing two hazard rates (independent groups):

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard rate in treatment</strong></td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Hazard rate in control group</strong></td>
<td>0.16</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Power (1 - )%</strong></td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Power (1 – beta)%</strong></td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Alpha error %</strong></td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Required sample size for</strong></td>
<td>81</td>
<td>32</td>
</tr>
<tr>
<td><strong>treatment group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Required sample size for</strong></td>
<td>81</td>
<td>32</td>
</tr>
<tr>
<td><strong>control group</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Statistical Methods:**

Frequencies and percentages were calculated for each group for all categorical variables. Mean and standard deviation were calculated for all continuous variables between the two groups. The mean scalp block duration was compared across the two groups using Mann Whitney U test. The categorical variables were compared across the two groups using Fisher’s Exact test or Pearson Chi Square test. The comparison of weight across the failed blocks was compared using independent t-test.
RESULTS
Results:

A total of 90 patients were recruited in this study between March 2012 and September 2012, 45 patients in each Group. Group 1 patients received 0.2% ropivacaine with 8 mg dexamethasone in the scalp nerve block after induction of general anaesthesia and Group 2 patients received plain 0.2% ropivacaine in the scalp nerve block. Six out of 45 scalp blocks were inadequate to obtund heart rate and blood pressure response to cranial pins.

Of these 6 failed blocks, 5 patients belonged to Group 2 and 1 patient to Group 1. Block duration could not be assessed in another 13 patients due to various reasons: 1 patient in Group 1 was not extubated, 1 patient in Group 2 had a post-op seizure, 1 patient in Group 2 underwent a re-craniotomy 4 hours post-op for raised ICP, 1 patient in Group 1 had features of raised ICP post-op and was conservatively managed and 9 patients (5 patients in Group 1 and 4 patients in Group 2) were inadvertently administered routine first dose analgesic on admission to the neuro-ICU without determining the VAS score. Hence, the block duration could be computed only for 38 (out of 45) patients in Group 1 and 33 (out of 45 patients) in Group 2.

Demographic data:

The baseline data comparing age, gender, weight, ASA status, surgery duration, pre-op VAS score and incidence of failed blocks between Group 1 and Group 2 are tabulated below:
### Table 5: Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=45)</th>
<th>Group 2 (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>27 (60%)</td>
<td>24 (53.3%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>18 (40%)</td>
<td>21 (46.7%)</td>
</tr>
<tr>
<td><strong>Age (mean ± standard deviation)</strong></td>
<td>40.2 years (± 10.99)</td>
<td>42.26 years (± 12.20)</td>
</tr>
<tr>
<td><strong>Weight (mean ± standard deviation)</strong></td>
<td>61.33 kg (± 10.01)</td>
<td>59.24 kg (± 10.45)</td>
</tr>
<tr>
<td><strong>ASA 1</strong></td>
<td>27 (60%)</td>
<td>20 (44.44%)</td>
</tr>
<tr>
<td><strong>ASA 2 and 3</strong></td>
<td>18 (40%)</td>
<td>25 (55.56%)</td>
</tr>
<tr>
<td><strong>Surgery duration (mean ± standard deviation))</strong></td>
<td>292.6 minutes (± 89.51)</td>
<td>285 minutes (± 78.99)</td>
</tr>
<tr>
<td><strong>Pre-op VAS (mean)</strong></td>
<td>4.06</td>
<td>3.74</td>
</tr>
<tr>
<td><strong>Failed blocks</strong></td>
<td>1 (2.22%)</td>
<td>5 (11.11%)</td>
</tr>
<tr>
<td><strong>Intra-op sugar (mean ± standard deviation)</strong></td>
<td>138.16 mg/dL (± 26.41)*</td>
<td>132.37 mg/dL (± 27.14)*</td>
</tr>
<tr>
<td><strong>Patients with post-op sugar &gt; 200mg/dL</strong></td>
<td>1 (2.22%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*n=25 in Group 1 and 30 in Group 2*
Sixty percent of patients in Group 1 (ropivacaine with dexamethasone in the scalp block) were males and 53.3% of patients in Group 2 (plain ropivacaine in the scalp nerve block) were males. The mean age of patients in group 1 (ropivacaine with dexamethasone) was 40.2 years and group 2 (plain ropivacaine) was 42.26 years. The mean weight of patients in Group 1 was 61.33 kg and group 2 was 59.24 kg. 27 (60%) out of 45 patients in group 1 (ropivacaine with dexamethasone) belonged to ASA grade 1 while the rest were categorised as ASA 2 or 3. 20 (44.4%) out of 45 patients in group 2 (plain ropivacaine) belonged to ASA grade 1 and the rest belonged to ASA class 2 or 3. As enumerated above, the distribution of age, gender, weight and ASA status seem comparable between the two Groups.

Intra- and post-operative random blood sugars were checked with a handheld glucometer in view of the concern of hyperglycaemia that could occur with perioperative steroids (all patients received oral/intravenous dexamethasone for 24 hours before surgery and for a few days post-op in addition to the perineural dexamethasone in the scalp block for Group 1 patients).

One patient in Group 2 had intra-operative sugars of 204 mg/dL which normalised to 150mg/dL by the conclusion of surgery without any treatment. Another patient in Group 1 had high post-operative sugars (serial readings >200mg/dL) requiring insulin although her pre-op random blood sugar was normal. She continued to require insulin throughout her weeklong post-op hospital stay and was asked to follow up in Endocrinology OPD for control of blood sugars if they remained high after discontinuing dexamethasone.
Comorbidities:

Among the ASA 2 and 3 patients in each group, the specific comorbidities are elaborated in the pie chart below. The category “others” includes cerebrovascular accident, ischemic heart disease and optic atrophy causing blindness.
Diagnosis:

The various diagnoses for space-occupying lesions in the brain for which the patients underwent supratentorial craniotomy are represented in the pie chart below. The category marked “others” represents Langerhan’s cell histiocytosis, Diffuse Large B Cell Lymphoma, epidermal cyst, neurocytoma, astrocytosis, oligoastrocytoma, hemangiopericytoma, tuberculoma, chondrosarcoma, inflammatory pseudotumour, gliosarcoma and one case of gliosis with no specific lesion.
Figure 6: Pie chart showing various diagnoses in Groups 1 and 2:

Site of craniotomy

The table 6 and Figure 7 show the distribution of sites of craniotomy between the two Groups. In Group 1, maximum number of patients underwent frontal craniotomy (26.67%) followed by parietal craniotomy (24.44%), while in Group 2, maximum number of patients underwent parietal craniotomy (26.67%) followed by frontal craniotomy (24.44%). Of special note is the number of patients who underwent temporal craniotomy including parieto-temporal, fronto-temporal and fronto-temporo-parietal craniotomies. This amounts to 14 patients in Group 1 and 17 patients in Groups 2. As temporal craniotomy is associated with muscle cutting, we analysed the association of unsuccessful scalp nerve blocks with the temporal site later in this dissertation.
### Table 6: Sites of Craniotomy in the two Groups:

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=45)</td>
<td>(n=45)</td>
</tr>
<tr>
<td>Frontal</td>
<td>12 (26.67%)</td>
<td>11 (24.44%)</td>
</tr>
<tr>
<td>Parietal</td>
<td>11 (24.44%)</td>
<td>12 (26.67%)</td>
</tr>
<tr>
<td>Temporal</td>
<td>8 (17.78%)</td>
<td>6 (6.67%)</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td>1 (2.22%)</td>
<td>0</td>
</tr>
<tr>
<td>Parieto-temporal</td>
<td>2 (4.44%)</td>
<td>4 (8.89%)</td>
</tr>
<tr>
<td>Fronto-temporal</td>
<td>5 (11.1%)</td>
<td>6 (13.3%)</td>
</tr>
<tr>
<td>Fronto-parietal</td>
<td>6 (6.67%)</td>
<td>5 (11.11%)</td>
</tr>
<tr>
<td>Fronto-parieto-temporal</td>
<td>0</td>
<td>1 (2.22%)</td>
</tr>
</tbody>
</table>
Figure 7: Site of craniotomy in both groups

Site of Craniotomy Group 1

- Frontal: 12 (26.67%)
- Parietal: 11 (24.44%)
- Temporal: 8 (17.78%)
- Parieto-occipital: 5 (11.10%)
- Parieto-temporal: 6 (13.33%)
- Fronto-temporal: 2 (4.44%)
- Fronto-parietal: 1 (2.22%)

n = 45

Site of Craniotomy Group 2

- Frontal: 11 (24.44%)
- Parietal: 12 (26.67%)
- Temporal: 6 (13.33%)
- Parieto-occipital: 5 (11.11%)
- Parieto-temporal: 4 (8.89%)
- Fronto-temporal: 6 (13.33%)
- Fronto-parietal: 5 (11.11%)

n = 45
Post-operative complications

The following representation summarises the incidence of post-operative complications that occurred in the two Groups:

Table 7: Post-operative complications in both Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=45)</th>
<th>Group 2 (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postop Fever</td>
<td>3(6.66%)</td>
<td>1(2.22%)</td>
</tr>
<tr>
<td>Postop seizure</td>
<td>2(4.44%)</td>
<td>2(4.44%)</td>
</tr>
<tr>
<td>Raised ICP</td>
<td>2(4.44%)</td>
<td>0</td>
</tr>
<tr>
<td>Re-craniotomy</td>
<td>0</td>
<td>2(4.44%)</td>
</tr>
<tr>
<td>Postop ventilation</td>
<td>1(2.22%)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes Insipidus</td>
<td>1(2.22%)</td>
<td>0</td>
</tr>
<tr>
<td>Toxic Epidermal  Necrolysis</td>
<td>0</td>
<td>1(2.22%)</td>
</tr>
</tbody>
</table>

Of particular interest was the incidence of post-operative fever because of the fear of scalp infection following multiple injection points while performing the scalp nerve block. However, none of the patients with post-op fever had scalp infection and in most cases, the fever spontaneously resolved within 24 to 48 hours after removal of
invasive catheters (urinary catheter, peripheral venous access, central venous access). Another worrisome complication of perioperative steroids is peptic ulcer bleed. Considering that Group 1 patients received dexamethasone in the scalp nerve block in addition to the routine perioperative oral and intravenous dexamethasone, we were pleased to note that none of the patients suffered from upper gastrointestinal bleeding.

**Primary Outcome:**

The primary outcome evaluated was duration of the scalp nerve block in both the groups, the duration being defined as time from administration of the nerve block till the time of first rescue analgesic post-operatively. The median duration of scalp nerve block in Group 1 (ropivacaine with dexamethasone) was 897 minutes (interquartile range 250 to 1890 minutes) and in Group 2 (plain ropivacaine) was 750 minutes (interquartile range 225 to 1940 minutes). Although it appears that the addition of dexamethasone to ropivacaine in the scalp nerve block prolongs the duration of the block, the result was not statistically significant (p value 0.804).

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BlockDuration (minutes)</strong></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td><strong>897</strong></td>
<td>250 – 1890</td>
<td>750</td>
<td>225 – 1940</td>
</tr>
</tbody>
</table>

IQR: Interquartile Range
Figure 8: Figure showing the primary endpoint in both groups.

Secondary Outcomes:

The following table summarises the secondary outcomes analysed namely intra-op anaesthetic requirements, time to emergence from general anaesthesia and incidence of PONV between the two groups:
Table 9: Summary of Secondary Outcomes:

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median intra-op fentanyl dose</td>
<td>2.00 (2.00-3.00)</td>
<td>2.00 (2.00-3.00)</td>
<td>0.775</td>
</tr>
<tr>
<td>mcg/kg (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postop nausea</td>
<td>2 (4.5%)</td>
<td>2 (4.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>vomiting (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to emergence</td>
<td>15.00 (9.25-20.00)</td>
<td>13.00 (10.00-15.50)</td>
<td>0.497</td>
</tr>
<tr>
<td>minutes (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients requiring propofol</td>
<td>21 (47.7%)</td>
<td>8 (17.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median propofol dose</td>
<td>2.0 (1.0-2.0)</td>
<td>0.47 (0-0.75)</td>
<td>0.015</td>
</tr>
<tr>
<td>mg/Kg (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IQR: Interquartile Range

1. **Additional intra-operative anaesthetic requirement:**

   It was hypothesised that addition of dexamethasone to the local anaesthetic would decrease anaesthetic requirements intra-operatively. As the general anaesthetic technique was standardised for all patients in both the groups, the additional anaesthetic requirement was assessed in terms of the additional dose of fentanyl
(in micrograms/kilogram body weight) and propofol (in milligrams per kilogram body weight) used to attenuate heart rate and blood pressure response during the surgery.

The median dose of fentanyl used in Group 1 (ropivacaine with dexamethasone) and group 2 was 2 mcg/kg. Propofol was used in 21% of Group 1 patients and 8% of Group 2 patients to attenuate heart rate and blood pressure response at various stages of the surgery. The median dose of propofol was 1.75 mg/kg in Group 1 (interquartile range 1.0 – 2.0 mg/kg) and 0.47 mg/kg in Group 2 (interquartile range 0.33 – 1.80 mg/kg). The dose of fentanyl between the two groups is similar and, hence, there is no significant difference with respect to intra-op anaesthetic requirement in this regard (p value 0.775). However, the dose of propofol used intra-op was higher in Group 1 and this difference is significant (p value 0.015 by Mann-Whitney U test for independent samples).

2. **Time to emergence from general anaesthesia:**

This was defined as the time from discontinuing the volatile agent till the time of extubation. The median time to emergence from general anaesthesia in Group 1 (ropivacaine with dexamethasone) was 15 minutes (IQR 9.25 – 20 minutes) and in Group 2 was 13 minutes (IQR 10 – 15.5 minutes). Although it appears that Group 1 patients took a longer time for emergence, the result was not statistically significant (p value 0.497 by Mann-Whitney U test).
3. **Post-operative Nausea and Vomiting (PONV):**

As dexamethasone has been shown to decrease the incidence of post-operative nausea and vomiting (65) when given in the intravenous form, it was hypothesised that Group 1 (ropivacaine with dexamethasone) would have less incidence of PONV compared to Group 2 (plain ropivacaine). Although the dexamethasone was given into the subcutaneous tissue in Group 1, some amount of this may have been absorbed systemically considering the highly vascular nature of the scalp. In each group, 2 patients out of 45 experienced PONV (4.5% in each group). There was no difference between the two groups in this regard.

**Sub analysis:**

1. In order to assess the quality of the scalp nerve block in the two groups, the median VAS prior to administration of the first post-operative rescue analgesic was compared between the two groups. The median VAS in Group 1 (ropivacaine with dexamethasone) was 6.0 (interquartile range 4 – 9) and in Group 2 was 7.0 (interquartile range 5 – 10). Although it appeared that the median VAS was lower in the dexamethasone group, the result was not statistically significant (p value 0.181).

2. **Table 10: Visual analogue scale scores prior to first rescue analgesic in Groups 1 and 2:**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS before</strong></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td><em>first analgesia</em></td>
<td><strong>6</strong></td>
<td><strong>4-9</strong></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

IQR = Interquartile range
3. Correlation of pre-op VAS with block duration: Assessment of pre-op VAS was done on the day prior to surgery by inflating a sphygmomanometer to 250 mmHg for 5 minutes and asking the patient to quantify the pain of cuff inflation on a scale of 0 to 10, with 0 implying “no pain” and 10 signifying “worst imaginable pain”. On comparing the pre-op VAS scores to the block duration, the following scatter plot was drawn up.

Figure 9: Scatter plot of pre-op VAS with block duration in Groups 1 and 2

It shows a slight negative slant (correlation coefficient of -0.11) implying a small, albeit statistically insignificant, correlation between pre-op VAS and block duration. The downward slant indicates that higher the pre-op VAS score, shorter the block duration.
4. **Correlation of failed blocks to temporal site of craniotomy:**

As temporal site of craniotomy is associated with more post-operative pain due to muscle incision compared to other sites (66), we wished to evaluate any correlation between temporal site of craniotomy and incidence of failed blocks. A failed block was defined as a scalp nerve block in which there was a significant heart rate and/or blood pressure response (heart rate rise of > 10 beats per minute and mean arterial pressure rise of > 10 mmHg) to cranial pins application and skin incision. There were 6 failed blocks, of which 1 failed block was in Group 1 and 5 were in Group 2. Of the 6 failed blocks, 3 patients had a temporal site of craniotomy and 3 did not as shown below.

**Table 11: Comparison of failed scalp nerve blocks with temporal and non-temporal sites of craniotomy in Groups 1 and 2**

<table>
<thead>
<tr>
<th>Temporal craniotomy</th>
<th>Group 1</th>
<th></th>
<th></th>
<th>Group 2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Failed block</td>
<td>Successful block</td>
<td>Total</td>
<td>Failed block</td>
<td>Successful block</td>
<td>Total</td>
</tr>
<tr>
<td>Temporal craniotomy</td>
<td>0</td>
<td>14</td>
<td>14</td>
<td>3</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Non temporal craniotomy</td>
<td>1</td>
<td>30</td>
<td>31</td>
<td>2</td>
<td>26</td>
<td>28</td>
</tr>
</tbody>
</table>

As the single failed block in Group 1 does not belong to a patient who underwent a temporal craniotomy, a Fisher’s Exact test was performed to assess a correlation between temporal site of craniotomy and failed blocks in Group 2 patients. It seems that there is a significant correlation between temporal site of
craniotomy and incidence of failed block in patients who belonged to Group 2 (p value 0.029 by Pearson Chi Square test).

5. **Correlation of failed blocks to patient weight:**

   The following table displays the mean weight of patients with and without failed blocks in Groups 1 and 2.

   **Table 12: Comparison of patient weight to failed scalp nerve blocks in Groups 1 and 2**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=45)</th>
<th>Group 2 (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed block (n=6)</td>
<td>75</td>
<td>57.40(±6.02)</td>
</tr>
<tr>
<td>Successful block (n=84)</td>
<td>61.02(±10.83)</td>
<td>59.48(±10.91)</td>
</tr>
</tbody>
</table>

   The weight of the single patient in Group 1 who had a failed block was 75 kg while the mean weight of the patients with successful scalp blocks in Group 1 was 61.02 (±10.83 standard deviation). The mean weight of the 5 patients with failed block in Group 2 was 57.40 kg (±6.025 standard deviation) while the mean weight of the 40 patients with successful scalp blocks was 59.48 (±10.91 standard deviation). Applying t-test for equality of means, the difference between weights of patients with failed blocks in Groups 1 and 2 does not appear to be statistically significant (p value for Group 1 was 0.209 and for Group 2 was 0.681).
6. **Block duration more than 240 minutes in Groups 1 and 2:**

The following table was computed to compare the patients in Groups 1 and 2 who had scalp block duration less than and more than 240 minutes. It seems that more patients in Group 1 (38) had block duration more than 240 minutes (4 hours) compared to Group 2 (32 patients). However, on applying Chi Square tests, the p value was calculated to be 0.465, and hence, this difference is not statistically significant.

Table 13: Comparison of patients with a scalp block duration of less than or more than 240 minutes in Groups 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block duration &gt; 240 minutes (n = 70)</td>
<td>38</td>
<td>32</td>
</tr>
<tr>
<td>Block duration &lt; 240 minutes (n = 1)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

7. **Block duration more than 360 minutes:** The table below displays the number of patients in both groups who experienced a scalp nerve block duration of more than 360 minutes (6 hours) in both Groups.

Table 14: Comparison of patients with scalp nerve block duration of less than or more than 360 minutes in Groups 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block duration &gt; 360 minutes (n =66)</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Block duration &lt;360 minutes (n =5)</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
From the above table, it seems that there are more number of patients (35) in Group 1 (ropivacaine with dexamethasone) who had a scalp block duration of more than 360 minutes compared to Group 1 (31 patients who received plain ropivacaine). It is to be noted that the number of patients with scalp block duration of less than 360 minutes is inclusive of the patients with scalp block duration of less than 240 minutes. However, this difference is not statistically significant (0 value 1.000 by Chi square tests).

8. **Block duration more than 480 minutes:**

The following tabulation denotes the patients in whom a scalp block duration of more than 480 minutes (8 hours) was recorded.

**Table 15: Comparison of patients with scalp nerve block duration of less than or more than 480 minutes in Groups 1 and 2**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 38)</th>
<th>Group 2 (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block duration &gt; 480 minutes</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>(n =50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block duration &lt;480 minutes</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>(n =21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The above representation reveals that more number of patients in group 1 was noted to have a scalp block duration of > 480 minutes (27 patients) compared to Group 2 (23 patients). It is worth noting that the numbers of patients included in the category which experienced a scalp block duration of less than 480 minutes are inclusive of the patients with scalp block duration of < 240 minutes and < 360 minutes. Although it seems that more number of patients in the ropivacaine with dexamethasone group had a longer duration of scalp nerve block, this difference was not statistically significant (0 value 1.000 by Chi square tests).
DISCUSSION
Discussion:

It appears that demographic data such as age, sex, patient weight and ASA grade, diagnoses and surgery duration are equally distributed between the two groups (45 patients each) and are, hence, comparable.

The duration of the scalp nerve block noted in both the Groups is 897 minutes in Group 1 and 750 minutes in Group 2. This is much longer than the duration of scalp nerve block reported with 0.75% ropivacaine used in scalp nerve block in other studies (571 minutes, reference 32). One reason for this could be that in some of these other studies, the scalp nerve block was given either after dural closure or just prior to extubation.

When Tuchinda et al\textsuperscript{33} performed scalp block with 0.5\% and 0.25\% bupivacaine prior to insertion of cranial pins, he measured time to first post op analgesic without including the surgery duration. In our study as well, the scalp nerve block was administered after induction of general anaesthesia and prior to cranial pinning. However, we defined our duration of scalp nerve block from the time of administration of the block until the time to request of first rescue analgesic post-operatively. Hence, this block duration would necessarily include the duration of the surgery. This would explain the longer duration of scalp nerve blocks noted in the evaluation of the primary outcome.

However, the study seems unable to conclusively assess the superiority of addition of dexamethasone as adjuvant to ropivacaine in scalp nerve blocks in terms of prolonging the duration of the scalp nerve block between the two groups. This is probably owing to the inadequate sample size incorporated in this study in view of time constraints to complete the dissertation.
The sample size calculated for power of 80% was 162 patients (81 patients in each arm). It was planned to recruit an additional 10% of patients (sample size 178) in view of the 7–10% incidence of post-operative complications in our neurosurgical patients, which would preclude the calculation of block duration.

Assessment of the secondary outcomes (intra-operative anaesthetic requirement, time to emergence from anaesthesia, incidence of post-operative nausea and vomiting) also yielded no statistically significant differences between the group that received ropivacaine and dexamethasone in the scalp nerve block and that which received plain ropivacaine.

Tuchinda et al\textsuperscript{33} showed a decrease in intra-op fentanyl requirements in patients who received 0.5% bupivacaine and 0.25% bupivacaine in the scalp nerve blocks compared to those who received normal saline in the scalp nerve block. Gazoni et al\textsuperscript{67} showed no difference in the mean concentration of intra-op sevoflurane and dose of remifentanil used in patients who received a pre-incision scalp nerve block with 0.5% ropivacaine when compared to patients who did not receive a scalp nerve block.

In our study, however, both the study and control groups did receive scalp nerve blocks albeit with different drugs. We could not prove a decrease in intra-operative anaesthetic requirement, with respect to doses of fentanyl and propofol used, in the group that received dexamethasone as adjuvant to ropivacaine when compared to the group that received plain ropivacaine in the scalp nerve block. Paradoxically, Group 1 patients (dexamethasone with ropivacaine in the scalp block) required more intra-op propofol to obtund response to surgical stimulation compared to Group 2. We are unable to furnish an explanation for this observation.
There was no difference in the time to emergence from general anaesthesia and post-op nausea and vomiting between the two Groups. This could probably be explained by the fact that all patients were already on peri-operative oral or intravenous dexamethasone. Hence, a single additional dose of perineural dexamethasone in the scalp nerve block does not provide any additional benefit.

The distribution of failed blocks seems uneven between the two groups of patients: 5 out of 6 patients with failed blocks belong to Group 2 and only 1 patient in Group 1. Hence, it is unlikely that comparison of failed blocks to patient weight (did more number of failed blocks occur in patients with greater body weight?) and comparison of failed blocks to temporal site of craniotomy (did more number of failed blocks occur in patients who underwent temporal craniotomy?) would be truly representative of the truth in this skewed distribution.

As patients who undergo temporal craniotomies are noted to have more pain due to splitting of the temporalis muscle, we wished to note if the failed blocks were due to the temporal site of the craniotomy. The sole failed scalp block in Group 1 did not have a temporal craniotomy while 3 out of 5 patients with failed block in Group 2 had temporal craniotomy. Hence, we were able to deduce that in Group 2 patients temporal craniotomy was associated with a higher incidence of failed block.

In other studies the concentrations of ropivacaine used was 0.75% and 0.5%. We used 10 ml of 2% lignocaine with 0.2 % of ropivacaine. We assessed the success of the block by the response to pin and skin incision. Since the Mayfield clamp is applied immediately after the block we hoped to get a faster action by adding 2%
lignocaine. We used a ring block for scalp infiltration rather than injecting at individual sites of the nerves alone. A ring block requires larger volume of local anaesthetic, and hence, we used lower concentration of ropivacaine. We felt that this concentration was sufficient for scalp nerve endings. We had successful block in 93.3% of patients using this concentration.

We also attempted to gauge if failed blocks were more in patients with higher body weight, owing to their larger head circumference. There was no difference in incidence of failed scalp nerve blocks between Groups 1 and 2 with respect to body weight. However, this may have been better studied if we had compared failed blocks to head circumference rather than to body weight.

The concern that dexamethasone given in the scalp block may be absorbed systemically and could result in steroid-related complications such as upper gastrointestinal bleeding and hyperglycemia was also addressed by checking random blood sugar with a handheld glucometer both intra-operatively and post-operatively in the ICU. In fact, two studies undertaken in patients undergoing awake craniotomy with scalp nerve blocks have shown a peak plasma concentration of levobupivacaine (used in the scalp block) at 12 minutes from the time of administration of the block and 15 minutes for ropivacaine\textsuperscript{69,70}.

It is, therefore, possible that dexamethasone administered in the scalp nerve block may be also absorbed systemically owing to the highly vascular nature of the scalp. Patients planned for supratentorial craniotomy receive a perioperative course of oral/intravenous dexamethasone (4 mg every 6 hours from one or two days prior to surgery for up to one week post-op, then taper and stop).
It was noted in this study that no patients suffered from peptic ulcer bleed in either Group. One patient in Group 1 had sugars above 200 mg/dL post-operatively in the ICU and required insulin till discharge although pre-op random blood sugar was normal. Another patient in Group 1 recorded an intra-operative blood sugar of 204 mg/dL which normalised without treatment toward the conclusion of surgery and remained so in the post-operative period. This underlines the importance of monitoring for steroid-associated side effects whenever a steroid is administered via any route.
CONCLUSIONS
Conclusions:

1. Addition of 8 mg of dexamethasone to 0.2% ropivacaine in scalp nerve blocks performed after induction of general anaesthesia for patients undergoing supratentorial craniotomies for intra-cranial space-occupying lesions does not prolong the duration of the scalp nerve block when compared to using plain 0.2% ropivacaine in the block.

2. Intra-operative fentanyl requirements appear similar in patients who received ropivacaine with dexamethasone in the scalp nerve block compared to those who received plain ropivacaine.

3. Intra-operative propofol requirements were significantly greater in patients who received dexamethasone in the scalp nerve block when compared to those who received plain ropivacaine.

4. There was no difference in the time to emergence from general anaesthesia between patients who received dexamethasone as adjuvant to ropivacaine in the scalp nerve block when compared to those who did not.

5. There was no difference in the incidence of post-operative nausea and vomiting between the patients who received dexamethasone as adjuvant in the scalp nerve block and those who received plain ropivacaine in the block.

6. There is no significant difference in the median VAS score prior to administration of first rescue analgesic between the two groups.

7. There was no significant correlation between a higher pre-op VAS as estimated with a sphygmomanometer inflated to 250 mmHg for 5 minutes and a shorter block duration across both groups of patients.
8. There was a statistically significant association between failed scalp blocks and temporal site of craniotomy in patients in whom plain 0.2% ropivacaine was used in the scalp nerve block.

9. There was no significant association between failed scalp nerve blocks and higher patient weight in both groups of patients.

10. There was no major complication associated with addition of dexamethasone as adjuvant to scalp nerve block.
LIMITATIONS OF THE STUDY
Limitations:

1. The sample size calculated to detect a significant difference (33%) in block duration between the 2 groups amounted to 81 patients in each arm. However, as only 90 patients were recruited (45 in each arm), the sample population studied was inadequate to assess the primary outcome.

2. Correlation of failed blocks could have been better assessed if compared to the head circumference rather than to body weight, especially when such a dilute concentration of ropivacaine (0.2%) was used in performing the block.
STRENGTHS OF THE STUDY
**Strengths of the study:**

1. This is a randomized double blinded prospective study involving 90 patients undergoing supratentorial craniotomy with 45 patients in each arm.

2. The topic of post-craniotomy pain is of prime interest to the surgeon and anaesthesiologist alike in view of the controversy involving the use of systemic analgesics such as opioids and their side effects that adversely affect intra-cranial pressure volume relationships and non-steroidal anti-inflammatory agents that may be inadequate in optimal treatment of severe pain. This study focuses on the use of a regional anaesthetic technique (scalp nerve block), that has been proved to decrease intra-operative anaesthetic requirements and delay time to use of first rescue analgesic in the post-operative period. However, the novel proposition of prolonging the effect of this noteworthy technique by addition of a glucocorticoid has been considered for the first time in this randomized control study.
References:


60. Yung-Wei Hsu, Jacques Somma, Yu-Chun Hung, Pei-Shan Tsai Chen-Hsien Yang, Chien-Chuan Chen: Predicting Postoperative Pain by Preoperative Pressure Pain Assessment. Anesthesiology 2005; 103:613–8


Bukk Yamaguchi Med School 56(3-4):21-31, 2009


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ANNEXURES
1. **PRE-INDUCTION**
   1. Arrange for MP 50 monitor to be brought to the theatre.
   2. Obtain the study number of the patient from the patient data sheet in the in-patient chart. Procure the envelope corresponding to the study number from the anaesthesia technician. The envelope will indicate the drug to be used in the scalp block, either ‘drug A’ or ‘drug B’, which will have been prepared by the pharmacy and will be available with the technician.
   3. Note the baseline heart rate and blood pressure (systolic, diastolic and mean) prior to induction, using the readings on the MP 50 monitor for all measurements.

2. **INDUCTION**
   After pre-oxygenation, use thiopentone 5 mg/kg or propofol 2 mg/kg for induction along with fentanyl 1-2 mcg/kg and vecuronium 0.1 mg/kg.

3. **MAINTENANCE**
   1. After intubation, maintain a minimum alveolar concentration of 0.8 – 0.9 and titrate dose of vecuronium infusion to maintain 2 twitches in train of four.
   2. Perform the scalp block bilaterally as described below:
      - Calculate the toxic dose of ropivacaine (3 mg/kg) and ensure that this is not exceeded in performing the block. Take 30 ml of 0.2% ropivacaine and 10 ml of 2% lignocaine in a bowl in the nerve block tray. Add adrenaline (8 divisions on an insulin syringe) to this 40 ml mixture to make 5 mcg/cc of adrenaline.
      - Aspirate the study drug (0.2% ropivacaine + 2ml dexamethasone or 2ml saline) from the vial.
      - Use a 22G Quincke needle attached to a 10cc syringe to administer the block subcutaneously at the following sites (1-2 ml at each site) after cleaning the skin with betadine-soaked gauze:
         a) Supraorbital Nerve : inject local anaesthetic superficial to the periosteum just above the supraorbital notch
         b) Supratrochlear Nerve : just medial to supraorbital nerve
         c) Auriculotemporal Nerve : 1.5 cm anterior to the tragus of the ear; inject superficially and subcutaneously after negative aspiration for blood.
         d) Zygomaticotemporal Nerve : at lateral border of orbit as well as field infiltration (extra 2 ml) above the zygoma through the temporalis muscle almost down to the periosteum of the temporal bone
         e) Lesser occipital Nerve : upper posterior border of sternocleidomastoid muscle
         f) Greater Occipital Nerve : subcutaneously inject alone the middle third of a line between mastoid process and external occipital protruberance along the superior nuchal ridge.
      - Perform the block bilaterally and inject drug the drug between the location of the nerves to produce a ring block.
4. INTRA-OPERATIVE MONITORING:

In the patient data record, kindly enter the patient details and hemodynamic parameters during specific stimuli during the surgery as tabulated.

Please treat any significant rise in blood pressure or heart rate with fentanyl (maximum 4 mcg/kg intra-op) or boluses of propofol (0.5 mg/kg per bolus). Please avoid use of beta blockers/alpha agonists as far as possible.

5. AT CLOSING AND EMERGENCE:

- Please note the heart rate and blood pressure during dura, bone and skin closing and at removal of cranial pins.

- Discontinue volatile agent (without tapering) after removal of cranial pins.

- Note the time from discontinuation of volatile agent to extubation and GCS at extubation.
PATIENT DATA SHEET

Number on the study envelope :

Drug code in envelope :

Number on the vial of study drug :

1. PATIENT DETAILS :

Date: 
Name: 
Hospital Number: 
Age: 
Sex: 
Weight: 
Diagnosis: 
Surgery: 
Site of incision: 
ASA: 
Comorbidity (if ASA II or III): 
Current medications: 
Time of administration of block: 

2. INTRA-OPERATIVE RECORD : Please note :
   - Blood pressure as systolic, diastolic and mean.
   - Significant rise in heart rate: > 10 beats rise during the event compared to just before the event
   - Significant rise in blood pressure: > 10 mmHg rise in mean blood pressure during the event compared to just before the event
<table>
<thead>
<tr>
<th>EVENT</th>
<th>TIME</th>
<th>HEART RATE (bpm)</th>
<th>BLOOD PRESSURE</th>
<th>Significant rise</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min post intubation</td>
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<tr>
<td>Cranial pins</td>
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<tr>
<td>Skin incision</td>
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<tr>
<td>Craniotomy</td>
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<tr>
<td>Dural opening</td>
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<tr>
<td>Other events evoking response</td>
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<td>Other events evoking response</td>
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<tr>
<td>Closing dura</td>
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<tr>
<td>Closing bone flap</td>
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<tr>
<td>Skin closure</td>
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<tr>
<td>Removal of pins</td>
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</tbody>
</table>

- a) Total opioid (fentanyl) used intra-operatively:
- b) Total propofol used intra-operatively:
- c) Any other drug used to treat significant rise in HR/BP, dose:
- d) Glucometer blood sugar intra-op:
- e) Time of completion of surgery:
- f) Time at which volatile agent was discontinued:
- g) Time of extubation:
3. **POST OPERATIVE RECORD**:
   - Please treat VAS score > 4 at any time postoperatively
   - No analgesic to be given unless patient requests or VAS > 4 or ICU doctor feels it necessary
   - First rescue analgesic to be intravenous paracetamol for all patients
   - Second rescue analgesic: any drug as per ICU protocol
   - Time of arrival in neuro ICU:

<table>
<thead>
<tr>
<th>TIME POST-OP</th>
<th>TIME</th>
<th>GCS</th>
<th>VAS</th>
<th>RESCUE ANALGESIA (DRUG)</th>
<th>RESCUE ANALGESIA (DOSE)</th>
<th>RESCUE ANALGESIA (ROUTE)</th>
<th>PONV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hour</td>
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<td>4th hour</td>
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<td>8th hour</td>
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<td>12th hour</td>
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<tr>
<td>24th hour</td>
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</tbody>
</table>

*Postoperative nausea and vomiting

- Time at first rescue analgesic:
- Time at 2nd rescue analgesic:
Patient Information sheet

A randomized trial comparing the effect of scalp block using ropivacaine alone or ropivacaine along with adjuvant dexamethasone in patients undergoing supratentorial craniotomy under general anaesthesia

You are being requested to participate in a study to see if a drug called dexamethasone along with drug ropivacaine when injected into your scalp at the start of your brain surgery can decrease the pain during and after your brain operation. The surgery is usually done with general anaesthesia alone or with general anaesthesia along with the scalp injection which is called a scalp block. It has been observed that even though surgery is done under general anaesthesia, during various stages of the operation, some pain is felt by the patient, which is seen as changes in the pulse and blood pressure by the anaesthetist. There are other drugs that can decrease the pain during surgery called opioids, but they have more side effects such as vomiting and drowsiness when compared to scalp block. We hope to include about 70 people from this hospital in this study.

What do these drugs do?

In this study, in addition to using a scalp block with a local anaesthetic ropivacaine, some patients will also get a dose of steroid along with this drug. This addition is said to make the pain relief last longer. This comparative study is being done to see this extra pain relief effect when additional steroid is used.

Does ropivacaine or dexamethasone have any side effects?

Ropivacaine has been used by many people all over the world to help reduce pain. The majority of people have not had any side effects. When used in much higher doses than we plan to use in this study, it can cause problems to the heart. Dexamethasone, as a single dose also does not have any major effects in otherwise healthy people; however, when used in diabetic patients, it can dangerous cause rise in blood sugar levels. In patients with high blood pressure, dexamethasone can cause persistent rise in blood pressure and in people with peptic ulcer disease, it can worsen their gastric symptoms; but these are usually not seen after a single dose of the drug.

If you take part what will you have to do?

If you agree to participate in this study, you will be randomized into one of 2 groups. Group one will receive drug ropivacaine for the scalp block and group 2 will receive dexamethasone in addition to ropivacaine for the scalp block at the start of the brain surgery. Neither you nor the anaesthetist will have a choice in whether you will be categorized into Group 1 or 2 as this will be decided by a
computer programme. Your reaction to pain during surgery will be assessed by the anaesthetist and after the surgery for the first 24 hours by the nurse in the Neuro ICU. You will be given pain killers as you require for pain by the ICU nurse and doctor. The nurse and doctor will know about the study being done, but they will not know what drug or drugs were used for you for the scalp block. Neither will you know what drug you have been given for the scalp block. You will have an equal chance of being in either group for the study. All other treatments that you are already on will be continued and your regular treatment will not be changed during this study. After the first 24 hours after surgery, all treatments and observations will be as per the routine for postoperative patients. No additional procedures or blood tests will be conducted routinely for this study.

**Can you withdraw from this study after it starts?**

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

**What will happen if you develop any study related injury?**

We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

**Will you have to pay for the study tablets?**

Only both drugs used for the scalp block and the anaesthetic drugs will be given free of cost. You will have to pay for the surgery, other drugs and postoperative care as per the hospital rules.

**What happens after the study is over?**

You may or may not benefit from the study drug that you are given. However, depending on the results of the study, others may benefit from the results.

**Will your personal details be kept confidential?**

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.
PATIENT CONSENT FORM

Study Title: A randomized trial comparing the effect of scalp block using ropivacaine alone or ropivacaine along with adjuvant dexamethasone in patients undergoing supratentorial craniotomy under general anaesthesia

Study Number:

Participant’s name:

Date of Birth / Age (in years):

I_____________________________________________________________ 

___________, son/daughter of  ________________________________

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I also understand that neither I, nor my doctors, will have any choice of what drug I will get [ ]

I also understand that the drugs used for the study will be provided free. [ ]

I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name:
Signature:
Date:

Name of witness:
Relation to participant:
Date: