



Research Article

A Randomised double blind clinical trial to compare the effects of preincisional infiltration of ropivacaine v/s bupivacaine on post tonsillectomy pain relief

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Abstract

Objectives: To determine whether pre incisional infiltration of ropivacaine will be effective in reducing post-operative pain intensity comparable to bupivacaine.

Patient & Methods: Prospective, randomised, double blind clinical trial at Lady Hardinge Medical College, ENT Department. Sixty children, aged 5-12 years, undergoing tonsillectomy were included in the study. Patients in one of the groups received 0.375% of ropivacaine infiltration in the tonsillar fossa while the other group received 0.25% of bupivacaine infiltration 5 minutes prior to incision. Wong Baker faces pain rating scale was used to compare two groups in respect of pain control. Unpaired student t-test were used to compare the two independent groups, $p < 0.005$ was considered statistically significant.

Results: In the postoperative hours there was a statistically significant pain relieving effect seen in ropivacaine group ($p < 0.0001$). in the other postoperative parameters such as nausea, fever, vomiting, bleeding, trismus, otalgia were not statistically different between two groups. There were no complications associated with ropivacaine or bupivacaine. No patients in the study suffered from any systemic side effects related to use of medication.

Conclusion: Locally infiltrating ropivacaine significantly relieves the pain of paediatric post tonsillectomy patients compared to equipotent dose of bupivacaine. Also ropivacaine is more effective to reduce postop analgesic requirement in the 1st hour and overall analgesic requirement.

Keywords: Tonsillectomy, Ropivacaine, Bupivacaine.

Introduction

Tonsillectomy is one of the most common paediatric surgery procedure practiced for 2,000 years, with varying popularity over the centuries.⁽¹⁾ The procedure is claimed in some books as "Hindu medicine" about 1000 BC (non-evidence based literature).

Palatine tonsils are the lymphoid tissue in oropharynx, constituting part of Waldeyer's ring, situated at the entrance of digestive and

respiratory system. These are immunologically most active between 3-10 years of age. Sore throat is a common presentation in children as tonsils are targets of infections, commonly caused by bacteria and viruses.

Tonsillectomy was traditionally performed for recurrent tonsillitis and its sequelae, but in recent times sleep disordered breathing has also emerged as one of the indication.⁽²⁾ Tonsils have a rich network of innervation and thus postoperative

pain is a significant cause of morbidity in tonsillectomy patients. Pain as a symptom is often undertreated as children often refuse to take analgesics, because either the drug is unpalatable or has side effects like nausea and vomiting. Children are more prone to the effects of post-operative pain because of which they are unable to maintain adequate hydration thus leading to suboptimal fluid intake, electrolyte imbalance and inadequate caloric intake. This further increases the chances of venous thrombophlebitis due to intravenous medication and supplementation. Thus hospital stay is prolonged resulting in higher chances of nosocomial infections and increased financial burden on the parents as well as the institution. Early post-operative pain remains a significant obstacle in the path of speedy recovery and smooth convalescence.⁽³⁾ It has been reported to have effects on clinical parameters leading on to negative outcomes such as anxiety, tachycardia, hypertension, poor wound healing and insomnia.⁽⁴⁾ Keeping in consideration the above problems, various attempts have been made to reduce the post-operative pain. Over the past two decades, there has been an increasing trend for infiltration of local anaesthetics both pre and postoperatively in the tonsillar region. The advantage of using infiltration anaesthesia technique is that it can provide adequate analgesia without any significant systemic absorption and disrupting normal bodily functions. When used in conjunction with other drugs local infiltration provides excellent pain relief along with significant reduction in rescue analgesic drug dosages. More recently modified infiltration techniques are being tried using nerve stimulators decreasing the dose of local anaesthetics.⁽⁵⁾ The drugs commonly used for infiltration are lignocaine, bupivacaine and ropivacaine.⁽¹⁵⁾ Bupivacaine (Marcaine, sensorcaine), is a widely used amide local anaesthetic and ropivacaine appears to be suitable for both epidural and regional anaesthesia, with a duration of action similar to that of bupivacaine and it seems to be even more motor-sparing than bupivacaine.⁽¹⁶⁾

Till date no study has been conducted on Indian population regarding comparison of post-operative pain relief by infiltration of ropivacaine and bupivacaine in tonsillectomy patients. The aim of our study is to compare the effects of preincisional infiltration of ropivacaine v/s bupivacaine on post tonsillectomy pain relief.

Patients and Methods

After obtaining Institutional Ethics Committee approval and written informed parental consent, 60 ASA I-II patients between 5 and 12 years of age, who were scheduled to undergo tonsillectomy were enrolled in this randomized, prospective and double blind controlled study. The indications for tonsillectomy were recurrent infections and tonsillar hypertrophy leading to obstructive symptoms. The exclusion criteria were hypersensitivity to sevoflurane, benzodiazepine, fentanyl analogues, propofol and components, acetaminophen, bupivacaine, ropivacaine, the presence of coagulation disorders and chronic diseases, regular use of analgesics, presence of analgesic use within 24 hours prior to surgery, presence of upper respiratory system infection, and the inability to understand the pain scales, being unable to communicate. After detailed history & examination patient underwent routine investigations namely, haemoglobin, total leukocyte count, differential leukocyte count, platelet count, prothrombin time, X-ray soft tissue neck—lateral view. The data was recorded on standard pro-forma. Informed consent from the guardian of the patient was taken.

Sensitivity to both bupivacaine and ropivacaine was tested prior to the procedure in both the groups. Ropivacaine is available in a dose of 0.75%, so to make the effects of drug equipotent ropivacaine was diluted with equal amount of normal saline. Thus ropivacaine 0.375% was used for infiltration.

Patient was kept fasting for six hours prior to surgery. All children were premedicated with midazolam hydrochloride 0.5 mg/kg orally (with maximum 25 mL of fruit juice) or intravenous

(IV) midazolam 0.05 mg/kg, 20 minutes prior to surgery. Patient monitoring included electrocardiography (ECG), non-invasive blood pressure (NIBP), and pulse oximetry (SpO₂). Anaesthesia was induced with 8% sevoflurane and after inserting the IV cannula, 2-3 mg/kg propofol. Oral endotracheal intubation was performed. The anaesthesia technique was standardized & uniform for all the patients. The study medications were prepared by a surgeon who was not involved in surgical management and postoperative follow-up. The anaesthesiologist who was involved in anaesthesia management and the postoperative follow-up, the surgeon, and the parents were all blinded to the treatment groups. The patients were randomly assigned to one of the two groups as DRUG A and DRUG B, by computer generated random tables from www.randomizer.org)

The solutions, 4 ml for each tonsillar fossa were given to the upper, lower, anterior and posterior poles of each tonsil at the same volume, by the same surgeon with a 23 G needle. No peritonsillar infiltration of adrenaline and/or ephedrine was administered. All surgical procedures were started five minutes after the peritonsillar infiltration and the surgeries were again performed by the same surgeon. The tonsils and capsules were dissected from extra-capsular surrounding tissues and removed by using scissors and dissectors. The haemorrhages were controlled with bipolar cauterization. Same dissection techniques were used for tonsillectomy in all cases.

After surgery no analgesics were given & patient was observed in a post-operative room for the

intensity of post-operative pain using **WONG BAKER Faces Pain Rating Scale** immediate post operatively, at 2 hours, 4 hours., 6 hours, 12 hours. 24 hours, 48 hours, 72 hours ---

1. At rest
2. While swallowing (on consumption of 100 ml of water; to be assessed after first 6 hours postoperatively as the patient is kept nil per oral during that period)
3. Any adverse effects/complications subsequent to the procedure were recorded.
4. Time to 1st rescue analgesic
5. Total dose of rescue analgesics

Rescue analgesics included acetaminophen in dose of 10 mg/kg per dose, subject to a maximum of 4gm. depending on the time of requirement it was given either intravenously or orally when **WONG-BAKER Faces Pain Rating Score ≥ 6** .

In view of the current study, valid and reliable assessment of pain is essential for both clinical trials and effective pain management. The nature of pain makes objective measurement impossible. Acute pain can be reliably assessed with tools such as WONG-BAKER pain FACES scale for both at pain rest and pain during swallowing. This scale has been used to measure analgesia following tonsillectomy in children.⁽¹⁸⁾

The score WONG-BAKER scale is a pain assessment tool consisting of facial expressions which represent the severity of pain experienced by the patient. It starts from 0 indicating no hurt to score 10 when it hurts the worst.

Wong-Baker FACES™ Pain Rating Scale



Statistical Analysis

Data were described with the use of mean± standard deviation [median (minimum maximum)] for metric variables. The chi-square test was used to compare groups for categorical variables. $p < 0.05$ was considered statistically significant.

Results

Sixty patients scheduled for elective tonsillectomy surgery due to recurrent infections and tonsillar hypertrophy leading to obstructive symptoms were eligible. The patients were randomly

assigned to one of the two groups. Among 60 patients who completed the study, 30 patients assigned to Group I (Drug A), 30 to Group2 (Drug B). In the demographic variables of the patients as in sex distribution is same in both the groups. (Figure 1) i.e. 66.67% are males and 33.33% are females. The age distribution pattern shows that majority of children for both the drugs belong to age group of 4-6 years (Figure 2), with mean age for drug A is 7.28 yrs. compared to 7.75 years in drug B.

Figure 1 Sex distribution

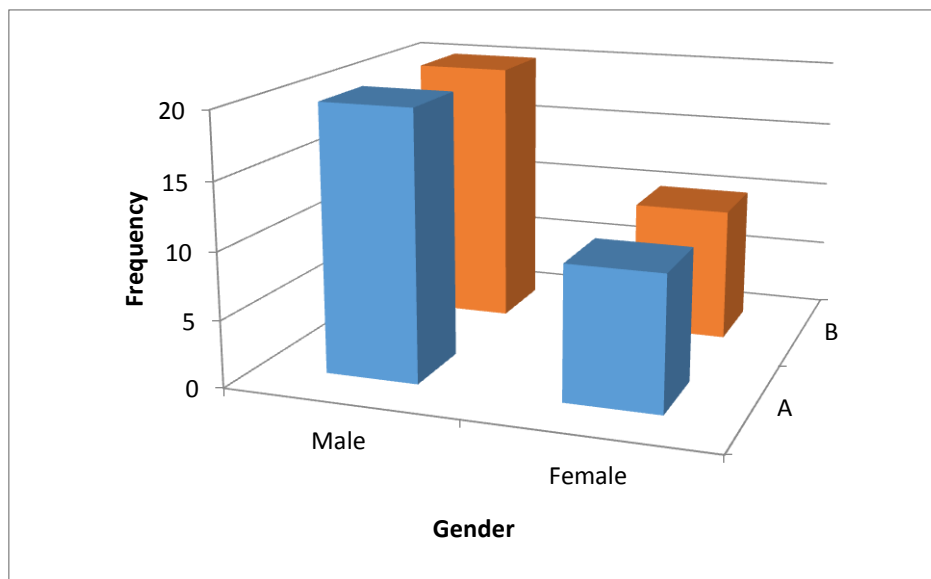
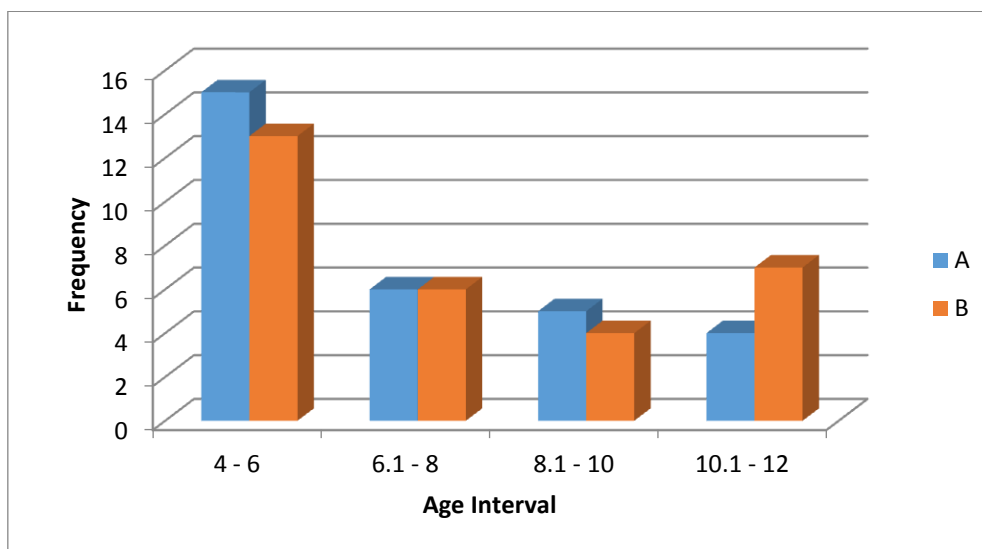


Figure 2 Age distribution



Line diagram (Figure 3) showing mean pain scores at rest for drug A and drug B immediately, at 2 hrs, at 4 hrs, at 6 hrs, at 12 hrs, at 24 hrs, 48 hrs and 72 hrs., that mean pain scores at rest are relatively higher for drug B compared to drug A with peak scores at 2 hours in both the groups. The p values for the standard deviation at various time intervals shows statistically significant result. Similarly at 6 hrs when the child was allowed liquids per orally i.e. 100 ml of water, mean scores were recorded till 72 hrs of hospital stay. The WBF pain rating score shows statistically significant scores with p value <0.0001. (Figure 4). The diagram depicts that the mean pain score with 100 ml of water intake is higher with drug B

compared to drug A. The scores are touching baseline and coming to level 0 in case of drug A at around 72 hours. The time to 1st rescue analgesic which is the pain that required acetaminophen administration developed immediately in 10% of children in Drug A group compared to 60% in Drug B group. Whereas, the mean time required for 1st rescue analgesic in children with drug A is 4.11 hrs compared to 1.92 hrs. In children with drug B with the difference in time of drug requirement is statistically significant amongst the two groups. The mean total dose in mg required by children infiltrated with Drug B (1038.50 mg) is significantly higher than in children infiltrated with Drug A (352.83 mg).

Figure 3 Mean pain scores at rest for Drug A and Drug B

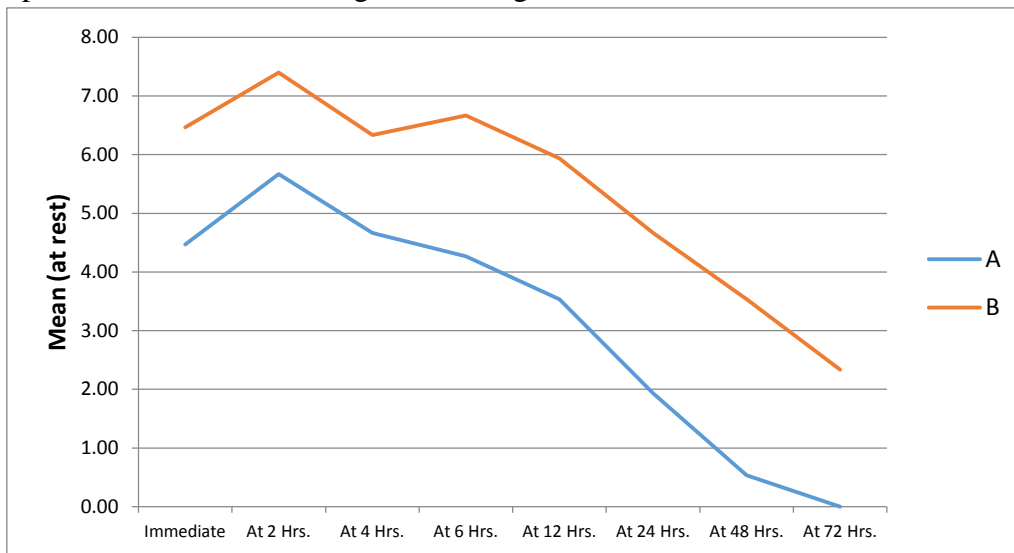
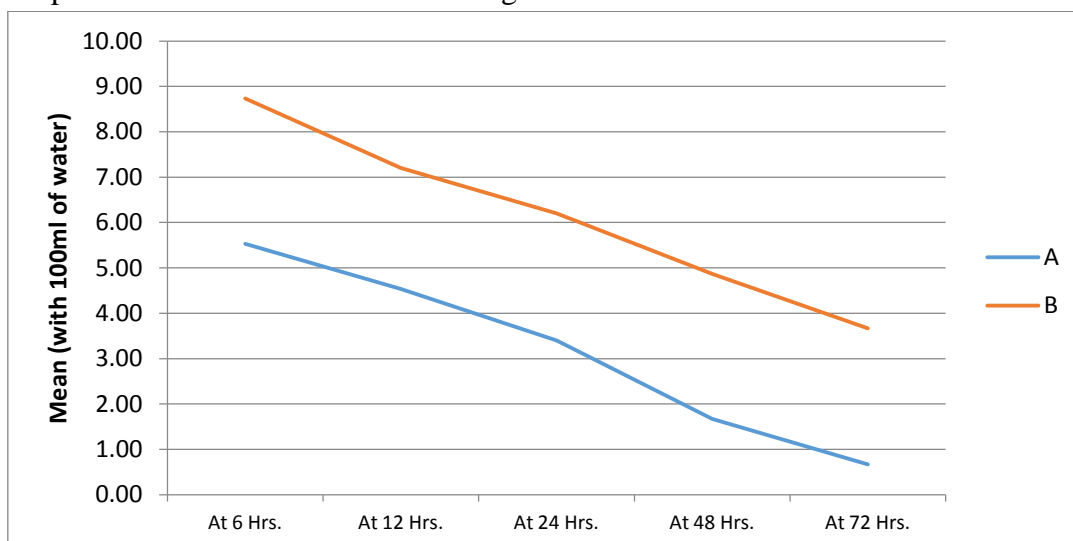


Figure 4 Mean pain scores at 6 hrs with swallowing of 100ml of water



Discussion

Tonsillectomy is one of the most commonly performed surgical procedures. There have been many advances in both surgical and anaesthetic techniques, which have resulted in faster operations and fewer post tonsillectomy complications. Nonetheless, pain after tonsillectomy remains an important problem. A number of different surgical and medical techniques have been studied in search for safe and effective post tonsillectomy pain relief.⁽¹⁹⁾

Trials have been conducted for studying the effect of local anaesthetic infiltration for post tonsillectomy pain relief but the results have been conflicting. This may be attributed to problems like inadequate sample size, different techniques, different timing of infiltration and varying concentrations of the drug. A few studies have included only adult population. So we conducted this study in an attempt to observe whether infiltration of local anaesthetic ropivacaine is actually beneficial compared to bupivacaine or not for reducing postoperative pain in patients aged between 5-12 years.

The hypothesis of our study was to compare the effect of preincisional infiltration of 0.375 % ropivacaine in the peritonsillar region with 0.25% of bupivacaine in decreasing the pain following tonsillectomy. We observed the pain, first at rest followed by pain on swallowing of 100 ml of water and pain was assessed with the help of Wong-Baker faces (WBF) pain rating scale. Pain at rest indicates the patient's comfort level. Decreased pain on swallowing ensures that the patient may have faster return to regular diet. We also observed the time taken for 1st rescue analgesic by the patient associated with total analgesic dose.

In our study we included a total of 60 patients planned for tonsillectomy without adenoidectomy. The study was focused on paediatric population (5-12 years) as tonsillectomy is being done most commonly in this age group and post tonsillectomy pain can be an annoying symptom in children. The subjects were equally distributed

in 2 groups of 30 patients each. In one group ropivacaine was infiltrated and in other group bupivacaine was infiltrated. Both the groups were randomly selected as drug A and drug B. the study was double blinded, both the patient and surgeon performing surgery did not know about the drug infiltration. Post-operative pain was assessed using Wong-Baker Faces pain rating scale. Pain was assessed immediately, at 2 hours, at 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours and 72 hours, both while at rest and on swallowing of 100 ml of water. It was found that pain in the drug A was significantly less at 4 hrs., ($p < 0.0001$) (only pain at rest is included at this time since the patient is not allowed orally before 6 hours following surgery) (Figure 4) , 6 hours at rest and on swallowing ($p < 0.0001$) compared to drug B.

In our study we have used preincisional infiltration of local anaesthetics to observe effects. Several articles have used post incisional infiltration of the drug which has resulted in measurable plasma levels but it does not reduce pain postoperatively and adversely effects the pain scores.⁽⁸⁾ Giannoni et al⁽⁷⁾ noted that preincisional injection of ropivacaine with clonidine prior to tonsillectomy provided decreased pain and opioid use and faster return to normal activity compared with placebo group in paediatric age group. Recent evidences suggests that surgical incision and other noxious perioperative events may induce prolonged changes in central nervous function which later contribute to post-operative pain.⁽²⁰⁾ The reason behind this technique is that the pain relief clearly cannot be explained by prolonged presence of the local anaesthetic in the area of surgery. This long lasting pain relief might be due to neural blockade which prevents nociceptive impulses from entering the central nervous system during and immediately after surgery and thus suppresses formation of sustained hyper excitable state responsible for the maintenance of post-operative pain. Local anaesthetics induce the antinociceptive effect by acting on the nerve membranes. However they

affect many membrane-associated proteins in any tissue. They can inhibit the release and action of agents sensitizing or stimulating the nociceptors and participating in inflammation (prostaglandins, lysosomal enzymes, etc.).⁽²¹⁾ Thus infiltration prior to incision gives the local anaesthetic sufficient time for action both by its local effect as well as central action.

Most commonly amide local anaesthetics are used for regional anaesthesia in paediatric population. These local anaesthetics are potent sodium channel blockers with marked stereo specificity, which affects their action. At toxic concentrations, they can induce arrhythmias with potential for cardiac arrest. These agents are bound to serum proteins and are metabolised by cytochrome P450. The intrinsic clearance of bupivacaine is lower compared to adults while that of ropivacaine is not as low as expected thus it can be used even in younger patients.⁽²²⁾

To our knowledge, there have been few reports comparing the efficacy and safety of ropivacaine and bupivacaine in post-tonsillectomy pain control with conflicting results. In the year 2006, Akoglu and colleagues compared the effects of 0.2% ropivacaine and 0.25% bupivacaine on post tonsillectomy pain during 24 hours of surgery.⁽¹⁰⁾ They concluded that 0.2% ropivacaine infiltration was a safe and effective method and equivalent to 0.25% bupivacaine for post tonsillectomy pain. According to trials of Unal et al⁽¹¹⁾ and Akoglu et al⁽¹⁰⁾, there is inadequacy of ropivacaine in preventing postoperative pain after tonsillectomy operations was due to low concentration of ropivacaine solution. So in our study, the concentration of ropivacaine solution was higher compared to above studies.

The other limitation of the studies by Unal et al⁽¹¹⁾ and Akoglu et al⁽¹⁰⁾ may be due to duration of postoperative pain assessment. These studies assess pain only for 24 hours but in our case study we kept a record of pain assessment for 72 hours postoperatively. Thus, prolonged pain follow up could be taken into account. In the present study the pain scores of the ropivacaine group (drug A)

were significantly lower both at rest and at time of swallowing at 4,8,12,24,48 and 72 hours. The adequately effective and prolonged pain relief is that the neural blockade prevents the nociceptive impulses from entering the CNS during and immediately after surgery and thus suppresses formation of sustained hyper excitable state that is responsible for the maintenance of postoperative pain.⁽⁶⁾

Some of the studies used epinephrine along with ropivacaine for infiltration. We did not prefer using epinephrine in conjunction with ropivacaine or saline as it is reported to have caused pulmonary oedema and intracranial haemorrhage following epinephrine infiltration for tonsillectomy (Tajima et al.1997).⁽²⁴⁾ A case of 16 year old girl who developed cardiac asystole and a central medullopontine infarct following combination of epinephrine with bupivacaine injection into tonsillar and adenoid bed has been reported (Alsarraf R, Sie K.2000).⁽²⁴⁾ Fortunately we did not detect any central nervous system or cardio toxic effects from infiltrating ropivacaine or bupivacaine.

One of the short comings of many studies was their small sample size and focus on adult population, as conducted in 2006 and 2008 by Arikan OK et al.^(9,12) was their small sample size and focus on adult population. Thus their results can't be compared with our study for paediatric age group. In contrast to our study the author also used epinephrine along with ropivacaine. Twenty adult subjects were given higher concentration of ropivacaine i.e., 2% ropivacaine and were assessed for pain at rest and while swallowing. Arikan OK et al, 2006⁽⁹⁾ did not use different patients instead they infiltrated one tonsillar fossa with ropivacaine and the other with saline in same patient. They found that the ropivacaine infiltration significantly reduced postoperative pain at rest and especially on swallowing till day 9. In our study we studied the patients for 72 hours and found that ropivacaine did offer significant pain relief beyond 48. The prolonged pain relief in the above study by Arikan OK et al,

2006⁽⁹⁾ might have been due to more concentration (2%) of ropivacaine as compared to 0.5% ropivacaine, as used by us. We did not prefer such a high concentration of the drug as our patients were children.

In the year 2008, the same author conducted a study for comparison of efficacy of preincisional high dose ropivacaine with bupivacaine for post tonsillectomy pain. Fifty eight adult patients were selected and divided in three groups for infiltration of ropivacaine, bupivacaine and saline. They observed preincisional infiltration of ropivacaine markedly reduced post tonsillectomy pain when compared with bupivacaine or placebo. Less amount of additional analgesic intake was also observed in ropivacaine group. In our case we used both the drugs in a double blind manner to make our results unbiased. Again the author had used epinephrine in all the three groups which we did not use in our study.

The above mentioned studies were mostly performed in case of adults for pain relief postoperatively, in the year 2011, Kasapoglu et al⁽¹³⁾ performed a prospective, randomised and placebo controlled trial comparing bupivacaine with its S- enantiomer levobupivacaine in children. The study was performed on 60 children, which concluded that both levobupivacaine and bupivacaine are effective than saline. The S- enantiomer and the racemate are equally efficacious and potent; however, both animal studies (Groban et al., 2001) and experience in humans suggest that levobupivacaine is less cardiotoxic.⁽¹⁵⁾

In a recent study by Mahmut et al in the year 2012, comparison of ropivacaine, bupivacaine and lidocaine in management of post tonsillectomy pain in children was done including 120 patients using a higher dose of ropivacaine 0.5% in comparison with 0.25% of bupivacaine and lidocaine. The study took into account intensity of pain as scored by visual analogue scale associated with other parameters like operative time, intraoperative blood loss, postoperative haemorrhage etc. the results showed ropivacaine

infiltration is as effective as bupivacaine for post tonsillectomy pain management in children but in view of potential side effects of bupivacaine epinephrine combination, ropivacaine is a safer choice, for post tonsillectomy pain relief.⁽¹⁴⁾

As per the guidelines of AAO HNS meeting in 2011 regarding indication of tonsillectomy⁽¹⁷⁾, perioperative and postoperative care, special emphasis has been given on importance of controlling the postoperative pain following tonsillectomy and recommends the use of appropriate measures for proper analgesia.

Our study has showed a reduction in the intensity of pain which was significant for early post-operative period up to 72 hrs. This local anaesthetic infiltration has resulted in significant reduction in duration and dosage of systemic analgesics associated with time to 1st analgesic. So it encouraged children to have adequate oral intake and thus, may shorten the hospital stay which also led to reduction in the risk of acquiring nosocomial infections and less financial burden for the institution and parents. Most of the patients in the Drug A had a relatively comfortable stay at the hospital and didn't have much of pain and difficulty in feeding as compared to most of the patients of Drug B. No complication was seen in patients receiving ropivacaine and bupivacaine. Thus the study concluded that Drug A ropivacaine is an effective and safer method for post-operative analgesia in paediatric age group.

Conclusion and Recommendations

With our study it can be concluded that preincisional infiltration of ropivacaine is safe and effective method of reducing post-operative pain up to 72 hours compared to bupivacaine in equipotent doses without producing any considerable side effects in patients ranging from 5-12 years and should be recommended for all the paediatric patients undergoing tonsillectomy so as to have a smooth, comfortable recovery and faster resumption of oral diet in the postoperative period.

Summary

- ❖ An open label randomized double blind study.
- ❖ Total of 60 patients were included in the study.
- ❖ Patients were divided in 2 groups of 30 patients each.
 - Group 1-BUPIVACAINE GROUP the patients in this group were infiltrated with injection ropivacaine 0.25% in the peritonsillar space 5 minutes prior to incision.
 - Group 2- ROPIVACAINE GROUP the patients in this group were infiltrated with injection bupivacaine 0.375% in the peritonsillar space 5 minutes prior to incision.
- ❖ Patients of both the sexes between ages 5-12 years were included in the study.
- ❖ Patients suffering from recurrent acute tonsillitis or chronic tonsillitis without adenoid hypertrophy posted for elective tonsillectomy were included in the study.
- ❖ Drug A consisted of 10 female and 20 male patients.
- ❖ Drug B consisted of 10 female and 20 male patients
- ❖ All the patients underwent a detailed history, examination and routine investigations.
- ❖ Sensitivity to ropivacaine was tested prior to the procedure.
- ❖ Sensitivity to bupivacaine was tested prior to the procedure.
- ❖ Informed consent from the guardian of the patient was taken.
- ❖ Patients were premedicated with oral midazolam 0.5mg kg⁻¹ and fentanyl 2mcg kg⁻¹ i.v.
- ❖ The patients were randomly divided into 2 groups one receiving Drug A and other receiving Drug B.
- ❖ Total dose of 0.375% of ropivacaine or 0.25% of bupivacaine was divided into 4

equal parts and infiltrated at four different sites in each tonsil

- ❖ Duration of 5 minutes was allowed for the onset of action of local anaesthetic prior to the incision.
- ❖ Dissection and snare technique was used for tonsillectomy in all cases.
- ❖ In the standard postoperative care, patients were not given any analgesic

The intensity of post-operative pain was assessed at immediately, 2hrs, 4hrs, 6hrs, 12hrs, 24hrs, 36 hrs, 48hrs, 72hrs post operatively using Wong Baker Faces pain rating scale (WBF) for the following parameters---

- 1. Pain at rest.
- 2. Pain while swallowing (on consumption of 100 ml of water; to be assessed after the first 6hrs postoperatively as the patient is kept nil per oral during that period)
- Time to 1st rescue analgesic
- Total dose of 1st rescue analgesic
- ❖ Scores were analysed with unpaired t-test and p values were calculated for each group for both pain at rest and pain on swallowing of 100 ml of water.
- ❖ Difference between the post-operative pain scores was statistically significant immediately, at 2 hours, at 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, and 72 hours for patients in group receiving ropivacaine compared to bupivacaine.
- ❖ Time required for 1st rescue analgesic is significantly late together with total dose of rescue analgesics in post-operative period in children infiltrated with ropivacaine.

Conclusion

Preincisional infiltration of ropivacaine is safe and effective method of reducing post-operative pain up to 72 hours without producing any considerable side effects in patients ranging from 5-12 years and should be recommended for all the paediatric patients undergoing tonsillectomy.

Bibliography

1. RA McNeill. A history of tonsillectomy: two millennia of trauma, haemorrhage and Controversy. The Ulster Medical Journal, 1960.
2. Mitchell RB et al. Sleep Disordered Breathing in Children: survey of current practice. Laryngoscope 2006; 116:956-8
3. Schoem S.R. et al. Control of Early Postoperative Pain with Bupivacaine in Paediatric Tonsillectomy. Ear Nose Throat J. 1993; 76:560-3.
4. Nalini Vedavelu et al. Recent Advances in Postoperative Pain Management. Yale J Biol Med. 2010 March; 83(1): 11-25.
5. Naja M.Z. et al. Modified infiltration technique in tonsillectomy: expanded case report of 25 children. Int J Pediatr Otorhinolaryngology (2005) 69, 35-41
6. Jebeles JA et al. The effect of preincisional infiltration of tonsils with bupivacaine on the Pain following tonsillectomy under general anaesthesia, randomized control trial. Pain. 1991; 47:305-8.
7. Carla et al. Ropivacaine with or without clonidine improves paediatric tonsillectomy pain. Arch. Otolaryngol Head Neck Surg .2001; 127: 1265- 1270
8. Park AH et al. Effect of perioperative administration of ropivacaine with epinephrine on post-operative podiatric adenotonsillectomy recovery. Prospective double blind randomized control trial. Arch Otolaryngol Head Neck Surgery 2004;130:459-64.
9. Arikan OK et al. Preincisional infiltration of tonsils with ropivacaine in post tonsillectomy pain relief. Double blind randomized, placebo controlled intra individual study. J Otorhinolaryngology 2006; 35:167-72.
10. Akoglu et al. ropivacaine compared to bupivacaine for post tonsillectomy pain relief in children: A randomized controlled study. Int J Pediatr Otorhinolaryngology (2006) 70, 1169-1173.
11. Yusuf et al. Comparison of bupivacaine and ropivacaine on post-operative pain after tonsillectomy in paediatric patients. Int J Pediatr Otorhinolaryngology (2007) 71, 83-87.
12. Arikan OK et al. High dose ropivacaine versus bupivacaine for post tonsillectomy pain. Prospective double blind randomized control trial .J Otorhinolaryngology-Head and Neck Surgery 2008;37:836-43.
13. Kasapoglu F et al. Comparison of peritonsillar levobupivacaine and bupivacaine infiltration for post tonsillectomy pain relief in children: placebo control clinical study. Int J Pediatr Otorhinolaryngology 75 (2011) 322-326
14. Mahmut O. et al. Comparison of ropivacaine, bupivacaine and lidocaine in the management of post tonsillectomy pain. Int J Pediatr Otorhinolaryngol. 2012 Dec; 76(12):1831-1834.
15. Goodman and Gilman's The Pharmacological Basis of Therapeutics 11th edition; 368,377.
16. Goodman and Gilman's The Pharmacological Basis of Therapeutics 11th edition; 247
17. *Otolaryngol Head Neck Surg.* 2011; 144: S1-S30.
18. Merry A.F. et al. Randomised comparison between the combination of acetaminophen and ibuprofen and each constituent alone for analgesia following tonsillectomy in children. Can J Anaesth. 2013 Dec; 60(12):1180-9
19. Robinson S.R. et al. Reducing post tonsillectomy pain with cryoanalgesia: a randomised control trial. Laryngoscope 2000; 110(7): 1128-1131
20. Katz J et al. pre-emptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. Anaesthesiology. 1992 Sep; 77(3):439-46.

21. Butterworth JF 4th and Strichartz JR. Molecular mechanisms of local anaesthesia: a review, *Anaesthesiology*, 1990; 72:711-734.
22. Mazoit JX et al. pharmacokinetics of local anaesthetics in infants and children. *Clin Pharmacokinet*. 2004; 43(1): 17-32.
23. Tajima et al. *J Clin Anesth*. 1997; 9:236-238.
24. Alsarraf R, Sie K. 2000 *Otolaryngol Head Neck Surg*. 2000; 122:572-573.