Analgesic effect of ketamine and morphine after tonsillectomy in children

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Abstract: A comparative double blind study of Ketamine and Morphine was conducted on eighty children following tonsillectomy to assess the analgesic, respiratory rate depressant and emesis. Children (6-12 years) were divided into two groups randomly (n=40). General anesthesia was induced followed by 0.1mg/kg morphine (I/M) and 0.5mg/kg ketamine (I/M) to Group I and Group II respectively before the initiation of surgical procedure. Pain scores (face score and CHEOPS score) were estimated for children at thirty, sixty, one hundred and twenty and two hundred and forty minutes following surgery. Comparison of CHEOPS score estimation reflected that pain scores were statistically significant ($P < 0.05$) in Group I receiving Morphine as compared to Group II who received Ketamine. The analgesic effect of ketamine and morphine showed statistically insignificant results ($P>0.05$) in case of face score. Moreover, respiratory rate in Group I had shown statistical association ($p<0.05$) as compared to the ketamine at 60 and 120 minutes. Furthermore, incidence of vomiting was more in Group I (0.05) as compared to Group II. It can be concluded from the study that ketamine may be used as a suitable substitute to that of morphine in children undergoing tonsillectomy.

Keywords: Analgesic, anesthetic, ketamine, morphine, opioids.

INTRODUCTION

Pain has been the companion of the mankind since the dawn of human existence. Efforts are being made to relieve pain in parallel with its perpetual existence. Pain is an unpleasant sensation related with tissue injury and may be referred to narrate such damages (Merskey, 1979). It is associated with severe discomfort, fear, autonomic changes, reflex activity and suffering (Willats and Logan, 1996) and is the most plausible reason to explain why patients seek help of physician. Postoperative pain can be differentiated from other varieties of pain because of its transitory nature and progressive improvement within short span of time; hence, it can be easily managed as compared to the chronic types of pain (Smith, 1996). However, postoperative pain was continued to be recognized, monitored and treated inadequate manners (Alexander, 1993), despite availability of new drugs and effective techniques (Fernando and Hunt, 1999). The poorly managed postoperative pain was realized by the Royal College of Surgeons and College of Anesthetist jointly in 1990 and suggested reforms for improvements, i.e., constitution of teams to treat acute pain; enhancement of resources for management and monitoring of pain relief and the improvement of education of medical staff and patients (Commission on the Provision of Surgical Services 1990). The disadvantages of inadequate controlled pain include pulmonary cardiovascular and thrombo-embolic complications leading to increased morbidity/mortality; delayed mobilization and prolongation in hospital stay (Ved *et al*., 1996). Hence the provision of optimal care for patients subsequent to surgery can be feasible only through effective pain relief.

Tonsillectomy is a very commonly done surgical method in children; however, the post-operative pain in children is usually difficult to manage (Penn, 1952). Many therapeutic modalities ranging from NSAIDs, systemic opioids and local anesthetics have been used in children as effective means for post tonsillectomy pain control in children (Wong *et al*., 1995). The opioids injections are most commonly used to manage most patients after tonsillectomy, based on the simplicity and practical applicability of the technique (Javery *et al*., 1996). Opioids analgesic also known as narcotic analgesic (Kalvey and Williams, 1997) cause respiratory depression, increased risk of lung, morbidity, sedation, nausea and vomiting, which may contribute to morbidity following tonsillectomy (Spence and Smith, 1998; Schug *et al*., 1998). Morphine is the proto-type of opioids though various new more potent than it is synthesized, it is morphine which represents the gold standard against which all other opioids are judged (Hendreson and Mcknight, 1997).

NSAIDs cause less drowsiness (Pierce and Fragen, 1990) respiratory depression (Watcha *et al*., 1992) and vomiting (Fitz-JamesI *et al*., 1995; Purday *et al*., 1996). They are useful in post-operative pain control and in the reduction of opioid requirement when used in combination with these drugs (Dahl and Kehlet, 1991; Souter and Fredam, 1994). NSAIDs inhibit the platelet function which may result in increased bleeding tendency during operation as well as post-operative period and should be avoided in

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Pain is assessed using both Eight Point Faces Scale (0=no pain-8=highest pain).

Faces rating scale (FRS)

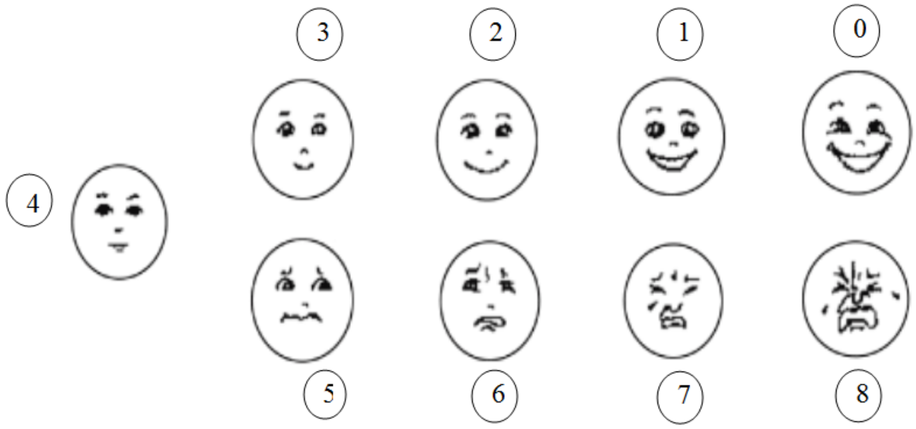

Fig. 1: Source: Escala de las nueve caras Tomada de McGrath *et al.*, 1996(98).

children after tonsillectomy (Bean *et al*., 1993) (Gunter *et al*., 1995). The choice of analgesic agents and technique for post-operative use depends on various factors like efficacy, convenience, cost and safety.

Ketamine is another drug that can be used in post tonsillectomy pain control in children. It is non-competitive antagonist at NMDA receptors and has analgesic properties in sub-anesthetic doses (Kochs *et al*., 1996; Roytblatt *et al*., 1993a). The most annoying limitations of ketamine are its adverse psycho-mimetic effect, including dizziness, depersonalization, frightening dreams and hallucinations but these are not common in low doses and appear to be very common in adults in comparison to children (Grant *et al*., 1995).

MATERIALS AND METHODS

It is a prospective, comparative, double blind study. This research was carried out after the approval from the Ethical Committee of Allama Iqbal Medical College. The technique applied in this study was similar to a study done in by RJ Marcus relating a comparison of Ketamine and Morphine after tonsillectomy for the assessment of analgesic effects in children (Marcus *et al*., 2000a). Patients were divided randomly into two equal groups of 40 subjects. Group I received Morphine and Group II received Ketamine, both groups having 40 patients. In inclusive criteria the children aged 6-12 years, ASA Grades I and ASA Grades II, are considered. Alongwith written consent from parent or guardian of the children admitted as inpatients for elective tonsillectomy is taken. Children in ASA Grade III and children below 6 years or above 12 years are placed in exclusive criteria. Patients with the history of allergic to morphine and ketamine and with the history of frequent nausea or vomiting and motion sickness are excluded from the study. Patient was preoxygenated with 4 liters of oxygen by putting mask on the mouth. General anesthesia was given with Propofal 3-3.5 mg/kg than Succinyl choline 1-1.5 mg/kg was given. Than endotreacheal tube was passed. Anesthesia was maintained with oxygen 33% Nitrous oxide 67% and Isoflurane 1-2.5%. The drug is diluted with distilled water to a concentration of Morphine 2mg/ml and Ketamine 10 mg/ml. After the induction of anesthesia but before the start of surgery 0.1 mg/kg Morphine or 0.5 mg/kg Ketamine was injected into the anterolateral region of the thigh intramuscularly by a third person.

The Children's Hospital Eastern Ontario Pain Scale (CHEOPS) (Score range is 4-13) is given below:

Cry	No cry Moan or cry Scream	1 2 3
Facial Expression	Smiling Composed Grimace	0 1 2
Verbal Response	Positive Non or other complaints Pain/or other complaints	0 1 2
Torso	Neutral Shifting/tense/shivering/uprig ht/strained	1 2
Hands	Not touching wound Reaching/touching/grabbing wound/restrained	1 2
Legs	Neutral Squirm/kinking/drawnup/tense d/restrained/standing/crouchin g/kneeling	1 2

Source: British Journal of Anesthesia, 2000; 84: 739-742.

The FACES and CHEOPS Scores were measured at ½, 1, 2, and 4 hours after removing the endotreacheal tube.

Adverse effects like nausea and vomiting were observed alongwith the respiratory rate at the same time. After 4 hours an inquiry is made about the occurrence of any dream or hallucinations. The duration of first demand of analgesia after tonsillectomy was also recorded. The time of the first demand of analgesia was also noted. Paracetamol (syrup) 15 mg/kg was administered as rescue analgesia. Parents are allowed to stay with the children overnight and were asked to fill a questionnaire on the morning following tonsillectomy. Inquiring about the nature of child's sleep and overnight dreaming and subject to rating of overall pain relief.

STATISTICAL ANALYSIS

Data collected from the study groups was analyzed by application of Kruskal-Wallis Analysis of variance and Mann-Whitney U-test to evaluate pain scores. For parametric data, Student's t-test and for categorical data Chi-square test of independence was applied.

RESULTS

The age of the respondents varies from 6-12 years and the mean age in Group-I (Morphine) was 9.90 and in Group-II (Ketamine) was 9.97. More than 50% of children fall in the age group of 12 in Group I & Group II. There were 65% (26) males in Group I. 35 % (14) females in Group II. Regarding the ASA Status, 80% (32) patients were in ASA I and 20% (8) patients were in ASA II in Group I, while in Group II 85% (34) was in ASA I. The mean weights of the patients were compared and show statistically no difference.

Timings at various stages were comparable in both groups. Time from induction of study drugs in both the groups showed no significant difference statistically. The time from study drugs given to start of surgery was compared and means values in Group I and Group II were 6.10 and 5.63 respectively. There was no difference of total time (t-independent test=0.986) of surgery of study drugs given in two groups. There is no difference of study drugs (t-independent test=0.853 and P-value=0.396) given in the two groups in relation to time from end of anaesthesia to extubation. Group I (Morphine) and Group II (Ketamine) did not show any statistically significant difference in time from extubation to eye opening on command. Time of rescue analgesia after extubation in the two groups with morphine and ketamine (t-independent test=1.788 and P-value=0.078) showed statistically no difference (table 1).

A comparison of the results of pain scores in both groups given morphine and ketamine was done. The results of pain score were compared in the both groups given morphine and ketamine. In faces scores at half an hour, 1 hour, 2 hour and 4 hour, no statistical difference was found between the morphine and ketamine with a mean rank of 44.50 and 36.50 at 30 minutes respectively (fig. 2). A significant statistically association was noticed between Group I and Group II for CHEOPS pain scores at half an hour, 1 hour and 2 hour with p-value of 0.044, 0.004 and 0.003 respectively. Pain scores related to face scores were compared and no association was found between two groups at 30, 60, 120, and 240 minutes (p-value>0.05). A significant difference was found between morphine and ketamine in CHEOPS pain score at the interval 30, 60 and 120 minutes (p-value of 0.04, 0.004, 0.003 respectively) (fig. 3).

Table 1: Demographic data and mean time of different events

Group	Morphine (N=40)		Ketamine (N=40)		Tests of significance and	
Variables	Mean/ Percentage	S.D	Mean	S.D***	t-test	p-value
Age in years	9.9000	2.0481	9.9750	2.0316	-164	0.870
Sex*	26(65%) males	14(35%) females	19(47.5%)	21(52.5%)	-	-
Weight	29.100	7.2529	29.8500	6.9265	-473	6.9265
ASA status**	32(80%) ASAI	8(20%) ASAII	34(85%)	6(15%)	-	-
Time from induction to study drug given	9.1000	1.7802	9.5000	2.481	0.829	0.410
Time from study drug given to start of surgery	6.100	1.7364	5.630	1.944	1.153	0.253
Total duration of surgery	23.500	3.3510	22.7500	4.0997	0.896	0.373
Time from end of anesthesia to extubation	7.63	2.733	8.1500	2.7693	0.853	0.396
Time from extubation to eye opening on command	4.1000	2.3837	4.4000	2.5500	-.544	0.588

*frequency, **frequency, *** Standard deviation

Table 2: Respiratory rates of the patients during different time intervals

Groups	Frequency	Mean at 30 min	Mean at 60 min	Mean at 120 min	Mean at 240 min
Morphine	40	22.2500	22.1750	21.4750	20.0000
Ketamine	40	21.5000	23.6250	24.2250	20.3500
Total	80	-	-	-	-
Test of significance and p-value		t-test=1.098, p-value=0.275	t-test=2.957, p-value=0.004	t-test=5.882, p-value=0.000	t-test=1.076, p-value=0.285

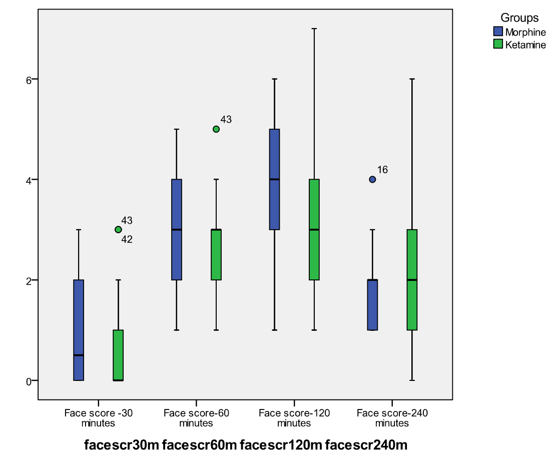

Fig. 2: FACES Scores at 30, 60,120 and 240 minutes.

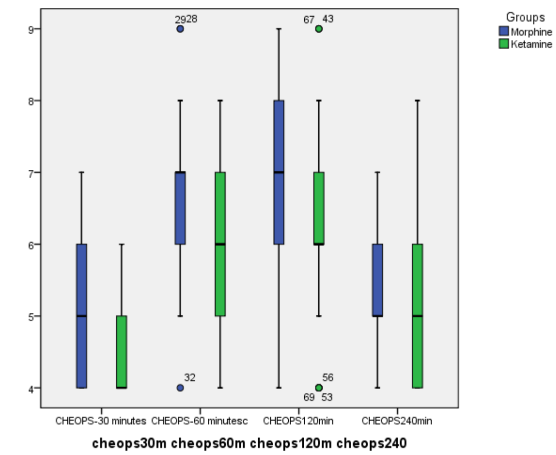

Fig. 3: CHEOPS Score at 30, 60, 120 and 240 minutes.

The respiratory rate at 60 and 120 minutes between the two groups showed a significant difference (p-value =0.004 and 0.000 respectively) but no statistical difference at 30 and 240 minutes (table 2). There was no significant statistical difference (Chi-square = 0.879 and P-value=0.348) between the group I and group II for rescue analgesia. Both groups I and II had statistical difference (Chi-square value=3.413 and P-value=0.06) regarding nausea but there was a statistically significant difference (Chi-square=5.591 and p-value=0.018) regarding vomiting in group I and II. The patients in group I and II having morphine and ketamine respectively did not show any significant difference (Fisher's Exact test=1.039 and P-value=0.308) regarding hallucinations. There was no difference of pattern of sleep and pattern of dream (Chi-square value=0.00 and P-value=1.000, Chi-square value=2.229 and P-value=0.328 respectively) among patients of two groups (table 3).

DISCUSSION

This study was conducted in order to compare analgesic effect of ketamine and morphine after tonsillectomy among children of 6-12 years of age. There was no statistically significant association was found in face scores at half an hour, an hour, two hours and four hours in patients (p-value=0.085, 0.402, 0.075 and 0.687 respectively) having morphine and ketamine (fig. 1) where as CHEOPS scores showed a marked significant difference at 30, 60 and 120 minutes (P-value 0.044, 0.004 and 0.003 respectively) in Group I and Group II (fig. 2). In this study, the pain scores related to facial expression and CHEOPS were higher in Group I as compared to Group II, however a study conducted by Marcus in United Kingdom the "face" pain scores are higher at 30 minutes in the ketamine group (p-value=0.05) than with morphine but were similar at 60, 120 and 240 minutes. These results are similar to our study except at 30 minutes where as in relation to CHEOPS, pain scores in Marcus study were higher at 30 minutes (p-value=<0.01) with ketamine as compared to our study in which pain scores are higher with morphine and they are statistically significant at 30, 60 and 120 minutes (Marcus *et al.*, 2000b). Another study was conducted to compare the effect of Ketamine and Fentanyl (a short acting opioid) on pain scores. It was concluded that no statistically significant difference between two groups at four interval of time for mean pain scores (p-value=0.05). Fentanyl is a small molecular weight opioid which is 75-100 times more potent as compared to morphine (Hafiz Oksu *et al.*, 2009). Whereas another study conducted in university of Ottawa, children were divided into two groups, Group I was given morphine and Group II was given morphine and ketamine, 0.25 mg/kg, at the start of Anesthesia and postoperative pain and pain scores were assessed with the

Table 3: Data showing Rescue analgesia requirement, Incidence of nausea, vomiting, hallucinations, Pattern of sleep and dream

	Morphine Group (M)		Ketamine Group (K)		Test of Significance and p-value
Rescue analgesia required	24(60%)	16(40%)	28(70%)	12(30%)	Chi-Square=0.879 P-value=0.348
Incidence of nausea	11(27.5%)y	29(72.5%)n	19(47.5%)y	21(52.5%)n	Chi-sq=3.413 P0.06
Incidence of vomiting	14(35%)y	26(65%)n	5(12.5%)	35(87.5%)n	Chi-sq=5.591 p-value=0.018
Respondents having hallucinations	1(2.5%)y	39(97.5%)	3(7.5%)	37(92.5%)	Fisher exact test=1.039 p-value=0.308
Pattern of sleep	32(80%)U	8(20%)	32(80%)	8(20%)	Chi-Square=0.000 P-value=1.000
Incidence of dreams	3(7.5%)Y	37(92.5%)N	7(18%)Y	33(82%)	Chi-square=2.22 P-value=0.38

help of Modified Children's Hospital of Eastern Ontario (mCHEOP) and adverse events were similar among the two groups (Abu-Shahwan, 2008).

The effects of ketamine and morphine on respiration shows statistically significant difference at 60 minutes and 120 minutes (P-value=0.004 and 0.00 respectively) but not at 30 minutes and 240 minutes (P-value 0.275 and 00.285 respectively) after tonsillectomy. Mean respiratory rate at 30 minutes were 22.25 and 21.50 respectively at 30 minutes where as in Marcus study mean respiratory rates were 20.5 in case of ketamine and 19.2 in morphine at 30 minutes after extubation with no significant association between two groups over the study period (i.e. at 60, 120 and 240 minutes after extubation). One of the important risk factors of opioids is respiratory distress after airway surgery (Virtaniemi *et al*., 1999; Marcus *et al*., 2000). There is always a critical debate on morphine for its long duration of action period, and delayed recovery period. Research is in progress for alternatives to morphine due to its side effects i.e. nausea and vomiting (Engelhardt *et al*., 2003). Ketamine is also an NDMA receptor antagonist may be beneficial in administration due to lack of observed respiratory depression (Verghese and Hannallah, 2005). Ketamine has a place in low doses as an opioids sparing agent and to improve the initial analgesia provided by NSAIDS (Eugene *et al*., 1997; Chia *et al*., 1997).

Regarding side effects with Morphine and Ketamine this study showed no statistically significant difference regarding nausea, hallucinations, sleep pattern and pattern of dreams respectively (0.06, 0.38, 1.00 and 0.38) but statistically significant difference between Group I and Group II was noticed regarding vomiting (p-value=0.018). There was low incidence of vomiting in the ketamine group in comparison to the morphine group. Another study conducted in Turkey to demonstrate the analgesic effect and other adverse effects due to morphine, ketamine and tramadol after adeno-tonsillectomy in children. It was noticed that in Group I who had received morphine the CHEOPS score was significantly low at 1, 5, 15 and 60 minutes as compared to the control group. The children having morphine took more time to have first analgesic doses as compared to children in ketamine and control group. Out of 60 children additional analgesic was taken by six children in group morphine, nine children in tramadol group, eleven in ketamine and 15 children of control group. Thus it was concluded that injection Morphine hydrochloride 0.1 mg/kg was given I/V during induction of anaesthesia shows a better analgesic effect in children undergoing adenotonsillectomy (Umuroglu *et al*., 2004).

In this study no statistically significant difference between Group I and Group II for need of analgesia after operation was found (Chi-square=0.879 and p-value=0.348). Another randomized prospective double blind study conducted in Turkey to assess the effects of ketamine in the prevention of postoperative pain after tonsillectomy. This study was done in 90 patients of age ranging from 5-15 years fulfilling the ASA physical status I and II criteria. It was noticed that postoperative analgesic requirements are decreased by ketamine and when used before surgery in tonsillectomy/adenotonsillectomy has analgesic effects (Aydin *et al*., 2007). Similar result was reported in another study in which children in ketamine group that required supplementary oral analgesia in the postoperative surgical units were few in number (Abu Shahwan, 2008).

Similarly another study was conducted in pediatric post operative patients on use of morphine infusions continuously following major surgeries like thoracic, abdominal or orthopedic surgery, among age group from 4 months to16 years. Morphine dose, pain intensity and side effects were noted at 3 hours intervals. Mean pain scores were 6.6 for CHEOPS in children upto 5 years of age. Episodes of emesis were found to be Emetic 36.7%. In girls the incidence of episodes of emesis was significantly higher in comparison to boys who might be related to the experience of pain as judged by visual analogue score. However opioid type side effects are common in those patients who are given high dose of morphine (Rugyte *et al*., 2007).

In another randomized study fifty children were pre-meditated with either ketamine 0.1mg i.m or placebo given 20 minutes before start of a standard general aneasthesia. It was concluded that there was no association in the sign of vomiting or dreaming in between the two groups (Elhakim *et al*., 2003). The reasons for this can be pre-operative anxiety which can effects in the young children undergoing surgery in relation to pain and behavioral recovery. This was confirmed by the study that pre-operative anxiety in young children undergoing surgery is due to a painful postoperative recovery and a more incidence of sleep and other related problems, so preoperative anxiety can be assumed as a limiting factor in this study (Kain *et al*., 2006). Patients having nausea more in case of Ketamine than Morphine and a higher incidence of emesis due to Morphine have been related to more pain (Kotiniemi *et al*., 1997; Andrews, 1992). We have seen in the results that the incidence of vomiting might be reduced in the ketamine in the absence of opioids and vomiting has not been noted as a problem in previous reports using analgesic doses of ketamine (Murray *et al*., 1987; Roytbiatt *et al*., 1993b). The etiology of vomiting after tonsillectomy is not precisely known, but is multifactorial. Pain, gastric irritation from swallowed blood, opioids use and a gagging feeling in the posterior oropharynx are possible contributing factors routine anti-emetics prophylaxis should be considered (Litman *et al*., 1994; Ferrari and Donlon, 1992).

Another prospective randomized controlled study was conducted in fifty children to evaluate the efficacy of a substitute analgesic to the use of opioids in providing analgesic effect in the immediately in postoperative period. Patients were randomized to receive either 0.1mg.kg-1 morphine or 0.5mg.kg-2 ketamine at induction. This study concluded that no additional side effects of ketamine were seen and ketamine was as effective as morphine (Aspinal and Mayor, 2001). Similarly another study done in Korea reported that ninety three children of aged 2-14 years having adenotonsillectomy, randomly divided into three groups and were given normal saline, 0.25mg/kg and 0.5mg/kg of ketamine respectively before the end of surgery. The results showed that there was a marked difference in modified CHEOPS among the three groups and 0.05mg/kg of ketamine group had a lower pain score in comparison to that of 0.25mg/kg ketamine (Lee *et al*., 2010). Ketamine acts as a potent analgesic at sub-anesthetic plasma concentration (Cha *et al.*, 2012).

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