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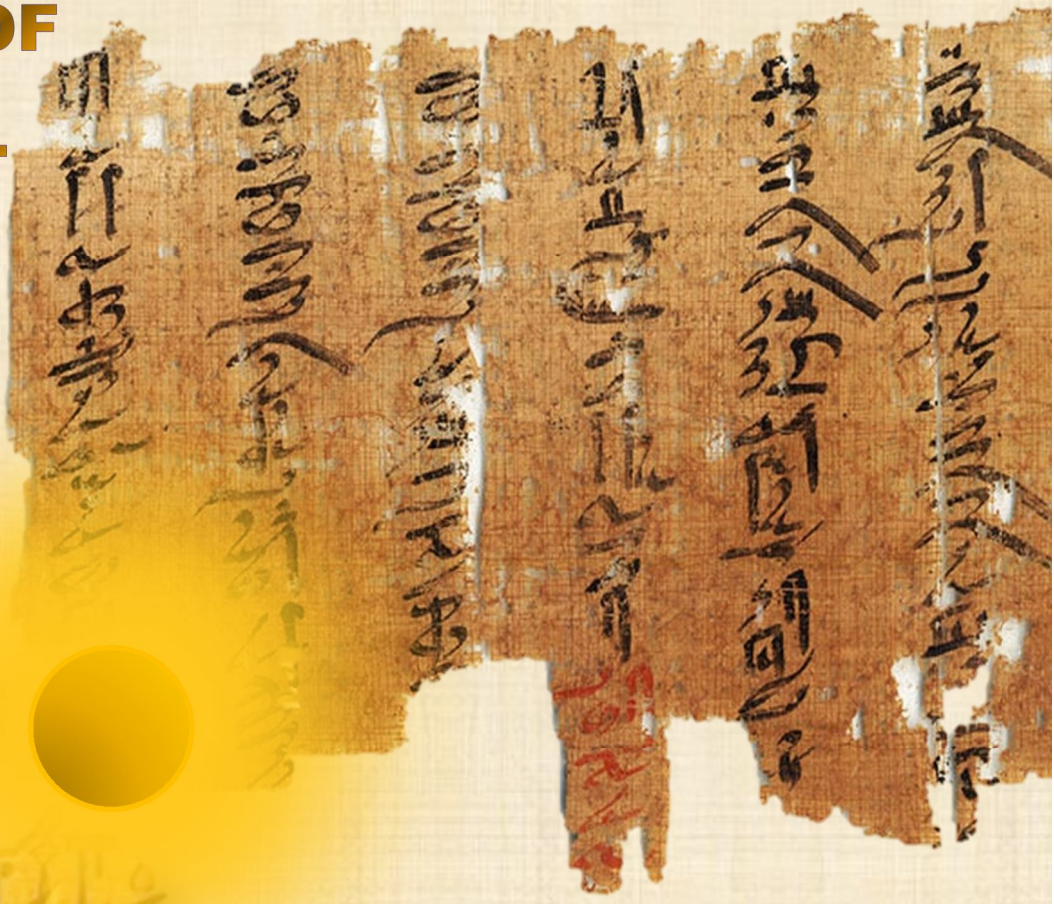

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Original article

Opioid Free Post-Operative Pain Management in Day Case Surgery of Tonsillectomy

Sabri A. Soltan[a], Nawal M. Alhulaimi[b], Mohsen M. Eissa [a]

Department of Anesthesia and Intensive Care, Faculty of Medicine, Al-Azhar University, Egypt[a]

Department of Otorhinolaryngology, Aljaber Hospital for Ear, Nose, And Throat, Alahsa, 31982, Kingdom of Saudi Arabia[b]

Corresponding author
Sabri A. Soltan
Email: sabrysoltan77@yahoo.com

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ABSTRACT

Background: Post-surgical pain is a challenging problem. Different modifications of surgical procedures and use of different analgesics had been reported. However, no consensus had been reached for post-surgical pain control. Tonsillectomy is one of the most commonly performed surgical procedure and pain control still controversial.

Aim of the work: To investigation safety and efficacy of intravenous paracetamol, ibuprofen, or both for post-tonsillectomy pain control.

Patients and Methods: The study had been carried at Otorhinolaryngology and Eye, Al-Jabr hospital, Anesthesia and Intensive Care Department in collaboration with Otorhinolaryngology department and the day care surgery unit], Al-Ahasa directorate, Kingdom of Saudi Arabia [KSA]. It included children aged 2 to 10 years. Patients had been randomly allocated into 3 equal groups [each 30 patients]. Group A [intravenous paracetamol 15mg/kg], Group B [intravenous ibuprofen 10mg/kg], and Group C [intravenous paracetamol 7.5 mg/kg and ibuprofen 5mg/kg]. The examined drug had been administrated 20 minutes after induction of general anesthesia. The analgesic effects and hemodynamics had been assessed on regular postoperative intervals till patient discharge, and patient satisfaction had been addressed. Any side effects and need for postoperative analgesia had been documented.

Results: Studied groups were comparable regarding patient demographics, recovery time, hospital stay duration and need for additional analgesia. However, pain was significantly variable between studied groups till 3 hours postoperatively. Pain was significantly reduced at groups B [IV ibuprofen] and C [IV paracetamol and Ibuprofen with reduced dose] when compared to group A [IV paracetamol] at all times. In addition, hemodynamic variability was observed for mean arterial pressure and heart rate. At five minutes, blood pressure was significantly higher in group B when compared to group C, and at 5 minutes to 2.5 hours, it was significantly increased among group A when compared to group C.

Conclusion: Drug combination with reduced [half the dose] of both intravenous paracetamol and ibuprofen is more effective and safer than single drug with higher dose. The studied drugs avoid the well-known side effects of opioids.

Keywords: Acetaminophen, Ibuprofen; Opioid-free, Drug combination, Post-tonsillectomy pain.

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Tonsillectomy with or without adenoidectomy is a frequent surgical intervention in children. For example, in United States, about 300000 procedures were carried each year [1,2]. The main indications are obstructive sleep disorders [especially in younger children], while in older children, the most common indication is recurrent tonsillitis [3].

Traditionally, tonsillectomy had been achieved as an inpatient procedure. However, there is a growing shift towards a day case procedure, with reduction of postoperative hemorrhage as the sole cause of shift. Other advantages include reduction prevention of unnecessary hospitalization, decrease of post-operative infection, cost effectiveness, decrease stress on both the patient and his/her family and prevention of psychological trauma. All these advantages were considered provided that, an excellent quality of care was provided, which achieved by advances in anesthesia and surgical procedure [4].

Tonsillectomy usually had marked postoperative pain [5,6], which represented a challenge to control, due to severity and duration of post-operative [post-tonsillectomy] pain. Pain control usually represented a main component of postoperative care [7]. In addition, there is a wide variation in pain management interventions, and there is yet no standard pain-relieving protocol [8].

Post-surgical pain management was practiced for a long time. However, it was practiced from humanitarian point of view, to alleviate suffering, till **Kehlet** [9] discovered the other benefits of postoperative pain relief, as it decreases the stress response after surgery and permits early mobilization. Traditionally, pain was alleviated by opioid administration. However, it is associated with respiratory side effects and potential for substance abuse, which restricted each use and stimulated search for another relatively safe analgesics [10].

Opioids remain the mainstay for postoperative pain management and provides its analgesics effect through their action within the central nervous system [CNS] [11]. But it did not interrupt the anti-inflammatory pain component. Interrupting inflammatory response to pain could decrease the overall need for analgesics especially opioids, and improve recovery [12,13]. Non-steroids anti-inflammatory drugs [NSAIDs] had been widely used as analgesics and anti-inflammatory. NSAIDs exerts their action through inhibition of arachidonic acid conversion to prostaglandins [14].

Paracetamol administrated in either oral or rectal formulations had long been used for the management of postoperative pain in children[15]; however its use is limited in post-tonsillectomy pain due to irregular bioavailability of rectal form and transient prohibition of oral form in post tonsillectomy patients[16]. Paracetamol had been considered as a preferred analgesic for post-tonsillectomy analgesia. However, its use is usually associated with inadequate analgesia. Non-steroidal anti-inflammatory drugs, on the other side, provide adequate postoperative analgesia, but the risk of bleeding is higher, and it could necessitate re-admission for bleeding control [17].

The use of a multimodal approach for postoperative pain management was considered an ideal approach aiming to increase efficacy and reduce side effects [18].

AIM OF THE WORK

The current study aimed to investigate the efficacy and safety of intravenous paracetamol, intravenous Ibuprofen and a combination of both drugs for post-tonsillectomy pain control.

PATIENTS AND METHODS

The study had been carried at Otorhinolaryngology and Eye, Al-Jabr hospital, Anesthesia and Intensive Care Department in collaboration with Otorhinolaryngology Department and the day case surgery unit], Al-Ahasa directorate, Kingdom of Saudi Arabia [KSA]. This hospital is 100 bed hospital capacity for both ophthalmology and Otorhinolaryngology patients, which serve for both emergency and elective cases and outpatients for all age groups and had four operating theaters and 6 intensive care unit [ICU] beds. The study included children aged 2 to 10 years, who presented for tonsillectomy with American society of Anesthesiology [ASA] score 1. On the other side, any child who had renal disease, hepatic disease, bronchial asthma, sickle cell disease, sickle trait or anemia [hemoglobin < 9 g/dl], had been excluded from the study.

Eligible patients were divided randomly into one

of three groups [each group included 30 cases]. Group A, for intravenous [IV] paracetamol 15mg/kg of body weight; Group B, for intravenous ibuprofen 10mg/kg of body weight, and Group C, for both drugs, but with reduced doses [IV paracetamol 7.5 mg/kg body weight and ibuprofen 5mg/kg body weight].

The examined drug had been administrated 20 minutes after induction of general anesthesia [GA]. General anesthesia was standardized for all patients and had been accomplished by IV propofol 2mg/kg body weight, IV fentanyl 1µg/kg body weight, and IV rocuronium 1 mg /kg of body weight].

The efficacy of studied drugs had been assessed. Analgesia had been assessed by pain assessment tool [WONG–BAKER FACES PAIN DESCRIPTIVE SCALE [FPS] in young children up to 6 years of age and older children assessed by verbal numerical pain [VNP] scale. The assessment had been started in post anesthesia care unit [PACU] every 5 minutes till discharge from PACU, then in every 30 minutes till discharge from day case surgery unit. In addition, side effects, such as bleeding, nausea and vomiting were assessed and documented. The length of hospital stay was calculated as the time since discharge from recovery till discharge from day case surgery unit. The patient satisfaction was measurement by the Glasgow Children's Benefit Inventory [GCBI], completed by parents and patients were categorized into two categories [satisfied or not]. The GCBI could be apply to any age and include 24 questions [4 dimensions, emotion, physical health, learning and vitality] [19].

The hemodynamic and respiratory parameters [hear rate [HR], blood pressure [BP], oxygen saturation [SPO2] and respiratory rate [RR]] had been assessed, and had been started in the post anesthesia care unit [PACU] every 5 minutes till discharge from the PACU, and then every 30 minutes till discharge from day case surgery unit.

According to need, additional analgesia had been administered in the form of Pethidine 1mg/kg, and had been documented.

Data analysis: Collected data were anonymized, and fed to personal computer. The statistical package for social sciences [SPSS], version 20 [IBM, SPSS Inc., USA] had been used for all statistical analyses. Data were expressed as arithmetic mean ± standard deviation [SD] if it was quantitative, number and percentage if it was qualitative. For quantitative data, One Way Analysis of Variance [ANOVA] was used as a test of comparison for the three groups, and post-Hoc LSD [least significant differences] were calculated to compare between two groups. Otherwise, Chi square test was used to compare qualitative data, and binary comparison had been carried out by Mann-Whitney [U] test. P value < 0.05 was considered significant.

RESULTS

In the present work, studied groups were comparable as regard to patient age, patient gender, recovery time, hospital-stay duration, need for additional analgesia or hospital admission and all patients were satisfied [Table 1]. No patient reported postoperative nausea, vomiting or bleeding.

On the other side, pain was significantly variable between studied groups at 0 time and till the end of the third hour post-operative. At 3.5 and 4 hours, no statistics could be computed as there was fewer than two groups. Pain was significantly reduced at groups B [IV ibuprofen] and C [IV paracetamol and Ibuprofen with reduced dose] when compared to group A [IV paracetamol] at all times. However, the difference between groups B and C was statistically non-significant [Table 2].

Both oxygen saturation and respiratory rates revealed non-significant difference between studied groups at any time [Table 3].

Results of the present work was significantly variable between studied groups at 5, 10, 15, 25, 30 minutes, and at 1.5, 2 and 2.5 hours. At five minutes, blood pressure was significantly higher in group B when compared to group C, and at 5 minutes to 2.5 hours, it was significantly increased among group A when compared to group C. In addition, heart rate was significantly increased in group A when compared to group C, from the basal time to 3.5 hours postoperatively. In addition, HR was significantly increased in group A when compared to group C from 25 minutes to 3 hours postoperatively [Table 4].

Table [1]: Patient characteristics and outcome [recovery time, duration of hospital stay and postoperative complications]

Parameter		Group A [Paracetamol]	Group B [Ibuprofen]	Group C [Both, reduced dose]	Test	P
Age [year]		4.73±1.98	5.06±1.87	5.43±1.71	1.06	0.35
Sex	Male	16[53.3%]	19[63.3%]	17[56.7%]	0.63	0.72
	Female	14[46.7%]	11[36.7%]	13[43.3%]		
Recovery time [min]		25.00±4.15	26.23±3.38	25.33±3.69	0.86	0.42
Hospital stay[hours]		3.06±0.28	3.18±0.35	3.20±0.38	1.32	0.27
PO nausea		0[0.0%]	0[0.0%]	0[0.0%]		
PO vomiting		0[0.0%]	0[0.0%]	0[0.0%]		
PO bleeding		0[0.0%]	0[0.0%]	0[0.0%]		
Need for additional analgesia		0[0.0%]	0[0.0%]	1[3.3%]	2.02	0.36
Need for hospital admission		1[3.3%]	0[0.0%]	0[0.0%]	2.02	0.36
Patient satisfaction		30[100.0%]	30[100.0%]	30[100.0%]		

Table [2]: Pain among studied groups at different postoperative times

	Group A		Group B		Group C		F	p
	Mean	S D	Mean	S D	Mean	S D		
Pain at 0 min.	1.47	0.89	0.60#	0.93	0.80#	0.84	7.73	0.001
Pain at 5min	2.00	0.74	0.60#	0.93	0.80#	0.85	24.13	<0.001*
Pain at 10min	1.47	0.90	0.60#	0.93	0.60#	0.81	9.62	<0.001*
Pain at 15min	1.33	0.96	0.53#	0.86	0.53#	0.81	8.23	0.001*
Pain at 20min	1.33	0.96	0.57#	0.89	0.46#	0.82	8.44	<0.001*
Pain at 25min	1.33	0.96	0.60#	0.93	0.26#	0.69	11.82	<0.001*
Pain at 30min	1.53	0.97	0.33#	0.76	0.13#	0.51	29.00	<0.001*
Pain at 1h	1.60	0.81	0.17#	0.53	0.13#	0.51	52.53	<0.001*
Pain at 1.5h	1.87	0.51	0.17#	0.53	0.00#	0.00	178.14	<0.001*
Pain at 2h	1.73	0.69	0.13#	0.43	0.00#	0.00	125.60	<0.001*
Pain at 2.5h	1.43	0.92	0.10#	0.32	0.00#	0.00	60.58	<0.001*
Pain at 3h	1.57	0.84	0.10#	0.31	0.00#	0.00	87.41	<0.001*
Pain at 3.5h	2.00	0.00					aa	
Pain at 4h	2.00	0.00					aa	

* significant; aa: no statistics can be computed as there is fewer than two groups; # significant decrease when compared to group A

Table [3]: Oxygen saturation and respiratory rate [RR] among studied groups

Variable	Time	Group A [Paracetamol]		Group B [Ibuprofen]		Group C [Both, reduced dose]		F	P
		Mean	S.D	Mean	S.D	Mean	S.D		
SO2	At 0 min	99.07	0.69	98.90	0.31	99.00	0.00	1.11	0.33
	At 5 min	98.80	0.76	98.67	0.48	98.73	0.64	0.33	0.72
	At 10 min	98.67	0.61	98.73	0.45	98.73	0.45	0.17	0.84
	At 15 min	98.53	0.63	98.57	0.50	98.60	0.50	0.11	0.89
	At 20 min	99.03	0.61	98.97	0.32	99.03	0.32	0.22	0.79
	At 25 min	98.87	0.63	98.90	0.48	98.80	0.48	0.27	0.76
	At 30 min	98.67	0.61	98.80	0.41	98.73	0.45	0.54	0.58
	At 1 H	98.57	0.63	98.60	0.50	98.63	0.49	0.11	0.89
	At 1.5 H	98.93	0.58	98.83	0.38	98.73	0.45	1.31	0.27
	At 2 H	98.60	0.72	98.73	0.45	98.73	0.45	0.57	0.56
	At 2.5 H	98.80	0.66	98.77	0.43	98.63	0.49	0.81	0.45
	At 3 H	98.79	0.69	98.60	0.50	98.63	0.49	0.88	0.42
	At 3.5 H	99.00	0.00	99.00	0.00	98.89	0.33	0.88	0.42
	At 4 H	99.00	0.00	98.75	0.46	99.00	0.00	1.23	0.32
RR	At 0 min	20.87	3.30	20.63	1.07	20.03	1.19	1.24	0.29
	At 5 min	21.10	0.66	21.27	0.91	21.03	0.89	0.63	0.53
	At 10 min	20.97	1.22	20.97	1.03	20.90	1.06	0.04	0.96
	At 15 min	21.00	1.11	20.97	1.22	20.90	1.06	0.06	0.94
	At 20 min	20.40	1.22	20.33	1.35	20.83	0.99	1.55	0.22
	At 25 min	20.87	1.17	20.83	1.93	20.40	1.07	0.98	0.38
	At 30 min	20.60	1.10	20.43	2.06	21.07	1.28	1.36	0.26
	At 1 H	20.47	1.28	20.37	1.19	20.90	0.71	2.03	0.14
	At 1.5 H	20.93	0.78	21.23	1.55	20.63	1.27	1.75	0.18
	At 2 H	20.13	1.11	20.83	1.51	20.40	1.22	2.25	0.11
	At 2.5 H	20.40	1.10	20.33	1.90	21.00	0.69	2.29	0.11
	At 3 H	20.14	0.85	20.57	1.68	20.67	1.40	1.20	0.31
	At 3.5 H	20.33	1.03	20.20	1.23	20.33	1.22	0.04	0.96
	At 4 H	21.00	0.00	21.33	1.03	20.71	0.76	0.85	0.45

Table [4]: Mean blood pressure and heart rate [HR] among studied groups

Parameter	Time	Group A [Paracetamol]		Group B [Ibuprofen]		Group C [Both, reduced dose]		F	p
		Mean	SD	Mean	SD	Mean	SD		
Mean BP	At 0 min	79.93	5.60	80.43#	5.51	77.10	5.83	3.04	0.053
	At 5 min	81.73$	4.62	80.47	5.13	78.10	4.91	4.27	0.017*
	At 10 min	82.60$	5.04	80.50	5.36	78.37	4.51	5.42	0.006*
	At 15 min	81.73$	6.43	81.13	5.87	78.30	4.37	3.19	0.046*
	At 20 min	82.13$	5.25	80.10	6.23	78.63	5.23	2.97	0.057
	At 25 min	82.20$	5.19	80.27$	5.82	77.53	4.13	6.35	0.003*
	At 30 min	81.36$	4.61	81.17$	6.45	77.47	3.88	5.45	0.006*
	At 1 H	81.20$	6.23	80.13	6.16	78.00	4.56	2.45	0.092
	At 1.5 H	81.67$	5.87	79.20	5.82	78.40	3.84	3.14	0.048*
	At 2 H	81.73$	4.26	79.90	5.63	78.60	4.72	3.10	0.050*
	At 2.5 H	82.40$	4.80	80.27	5.56	78.47	4.63	4.63	0.012*
	At 3 H	81.93	3.66	80.63	6.48	79.40	4.04	1.92	0.15
	At 3.5 H	80.00	0.00	78.22	3.63	81.20	4.39	1.36	0.28
	At 4 H	80.00	0.00	78.43	2.44	79.67	4.41	0.30	0.74
HR	At 0 min	108.87$	9.22	107.63$	10.69	101.93	9.99	4.11	0.02*
	At 5 min	108.27$	8.32	108.63$	9.97	102.97	8.81	3.68	0.03*
	At 10 min	108.93$	8.31	108.21$	10.35	101.30	8.94	6.24	<0.001*
	At 15 min	107.87$	8.60	106.53$	9.02	100.63	9.09	5.61	0.01*
	At 20 min	108.79$	7.53	106.07$	8.81	100.50	8.19	7.74	<0.001*
	At 25 min	108.53$@	6.75	104.40$	8.00	99.30	8.63	10.46	<0.001*
	At 30 min	109.00$@	6.20	102.80$	9.74	98.57	7.77	12.80	<0.001*
	At 1 H	108.80$@	7.38	102.30	9.40	99.33	7.48	10.62	<0.001*
	At 1.5 H	109.27$@	7.36	102.20$	8.02	98.20	6.33	17.83	<0.001*
	At 2 H	108.53$@	7.17	101.83$	7.98	96.53	6.44	20.79	<0.001*
	At 2.5 H	108.87$@	6.32	100.20$	7.79	96.27	5.06	29.62	<0.001*
	At 3 H	106.86$@	7.93	100.17$	7.57	96.17	5.61	16.72	<0.001*
	At 3.5 H	100.33	4.59	103.00	7.36	97.78	5.52	1.70	0.21
	At 4 H	95.00	0.00	102.33	3.14	96.71	8.01	1.85	0.20

$ Significant increase when compared to group C; @ significant increase when compared to group B.

DISUCSSION

The post-tonsillectomy pain had great importance, as it may be associated with long duration of hospital stay, and re-hospitalization for pain management by intravenous analgesics [20]. Previous literature had many trials investigating different drugs [opioids, non-opioids, steroids and others] administered in different routes [oral, intravenous, subcutaneous and infiltrations], to alleviate post-tonsillectomy pain [21,22]. However, no standard regimen was identified. Thus, the present work designed to search for a better protocol for pain relief after tonsillectomy. We used intravenous route to achieve rapid pain relief and confirm the arrival of all assigned dose to the systemic circulation. Paracetamol and ibuprofen were selected to avoid potential complications of opioids, mainly respiratory depressions [23,24]. Pain relief and stable hemodynamics were significantly better in combined drugs with reduced dose, followed by ibuprofen and finally paracetamol. However, patient satisfaction had been reported by all children in all the three groups.

IV ibuprofen had been approved by the Food and Drug Administration [FDA] in 2009 for the treatment of mild to moderate pain as a separate drug, and in conjunction with opioids in treatment of moderate to severe pain in adults. The IV ibuprofen had been extended to pediatric patients [≥6 months] [25]. The main concern about NSAIDs use was about postoperative bleeding. A Cochrane review concluded that, NSAIDs are safe and did not significantly alter coagulation profile when compared to placebo or other analgesic drugs. The only exception is ketorolac, which had been associated with significant bleeding in post-tonsillectomy patients [26]. In addition, **Bidwell et al.** [27] confirmed the safety of NSAIDs in post-tonsillectomy emergency department, when used in combination with acetaminophen. This study also signifies the effectiveness of ibuprofen-acetaminophen regimen, to be equally effective as well as acetaminophen-

codeine combination, and bleeding had been not increased with the use of such regiment.

The adequate analgesia is the most significant desired outcome by parents and their children. However, the safety profile and possible side effects must be addressed. Side effects were minimal or absent in the current work. Nausea and vomiting were absent, respiratory depression, urinary retention, constipation or pruritus had not been reported. A study by **Kelly et al.** [28] compared the safety and efficacy of ibuprofen versus morphine for post-tonsillectomy pain, and reported that, postoperative comorbidities are significantly higher with morphine especially respiratory side effects. Hypercarbia seen in sleep disordered breathing of children may increase the delivery of opioids to CNS, with potential increase of respiratory complications. **Moss et al.** [29] used intravenous ibuprofen [10mg/kg] prior to anesthesia, aiming to achieve the optimal concentration at the arrival of child to post-anesthesia care unit, and concluded that, this regiment significantly reduced the use of fentanyl with increased safety profile.

Paracetamol is a commonly used analgesic, with high safety profile in children. It had lower side effects than NSAIDs [14,30], and usually used as a first line for post-tonsillectomy pain [31]. **Suters and Isaacson**[32] reported that, when used as a mono-therapy, paracetamol seems to be insufficient for post-tonsillectomy pain, and recommended its use in combination with NSAID or opioid for optimal pain control [the results which confirmed in the current study]. However, **Kocum et al.** [33] concluded that, IV acetaminophen is found to have a similar analgesic effects as IV dipyrone in pediatric day-case tonsillectomy.

The safety and efficacy of combined ibuprofen and paracetamol combination had been widely studied among adult populations and evidence strongly supporters the drug combination over the mono-therapy[34,35]. In a pediatric trial, the preoperative ibuprofen 5 mg/kg alone or combined with paracetamol 15 mg/kg had been associated with lower dental pain and distress scores, when compared to paracetamol alone, 15 minutes after recovery form general anesthesia [36].

In 2002, Pickering et al. [37] reported a significant delay of postoperative analgesic request and reduction in total number of children need additional analgesia with the use of preoperative paracetamol 20mg/kg plus ibuprofen 5mg/kg, when compared to paracetamol alone. On the other side, **Merry et al.** [31] compared paracetamol [12mg/kg] to ibuprofen 5mg/kg and combination therapy and reported that, there was no clinically significant changes were observed between groups especially for pain score.

Constant et al. [8] concluded that, paracetamol and ibuprofen should be considered as the "workhorse analgesics" for post-tonsillectomy pain. **Cohen and Sommer** [1] reported that, caution with the use of NSAIDs must be considered, and NSAIDs should be avoided if there is a positive history for coagulopathy, recurrent bleeding, renal dysfunction, peptic ulcer or allergic reactions. Thus, a use of drug combination with reduced dose of both drugs appears to be a good alternative, which is more efficient in reduction of pain and decrease potential side effects.

From the current and previous studies, the effectiveness and safety of drug combinations [IV paracetamol plus IV ibuprofen] had been confirmed. The current doses [7.5 mg/kg and 5mg/kg for paracetamol and ibuprofen respectively; a unique for the current study] seems to be the optimal dosing for pain control after day-case tonsillectomy. This regimen should be considered for application as a "corner stone" in pain management post-tonsillectomy in day case surgery. However, there are some limitations of the current study: first is the small sample size, second: the younger age of studied children, which could affect their pain expression and their requests for pain medications. The third limitation is the short duration of follow up, which could not be avoided due to study design and surgical technique.

Anyway, the current work proves the safety of day-case tonsillectomy with effective pain control when used either intravenous paracetamol, ibuprofen or a drug-combination with reduced dose. Drug commination was more effective and safer. Future studies are required to globalize the results of the current work.

Financial and Non-Financial Relationships and Activities of Interest

Authors declare that, there was no financial or non-financial relationships or activities of interest. The research was fully funded by researchers.

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