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A Comparative Study of Hemodynamic Effects of Remifentanil with or without Atropine in Pediatric Day Case Surgery

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Abstract: Background: Remifentanil is a short-acting opioid which is suitable for short-duration procedures such as bone marrow aspiration and biopsy; it's known to cause bradycardia and hypotension; pre medicated of Atropine is important to decrease the incidence of bradycardia and hypotension. **Aim of the study**: to evaluate the hemodynamic effect of Remifentanil during bone marrow aspiration and biopsy in children with or without atropine. **Methods**: This is a prospective randomized, double-blind study included Eighty children .who were scheduled for B.M.A. they were allocated in two groups, forty children received atropine (group A), and forty received normal saline (group N) the H.R. and B.P. (S, D, M,) were monitored and recorded at specific time intervals: At induction before Remifentanil given, at time of Remifentanil given, T3, at recovery (T. 6, T.9, T.12, T. 15) and at time of discharge. All children received Remifentanil 1 µg/kg. They injected over 30 Sc, a period followed by an infusion of 0.01 µg/kg/min. **Result:** Remifentanil cause a significant decrease in heart rate compared with the time of Remifentanil given, which is greater at (T.3) in the two groups. However, the values at recovery time (T.6, T.9, T.12, T.15) and at the time of discharge are highly significantly different between the two groups. In comparison with (T.3), there was a significant fall in B.P. (systole and mean), the values at recovery (T.6, T.9, T.12, T.15) and at the time of discharged are significantly different in the two groups in which P value less than 0.01 means highly significant. And P. Value between 0.02-0.05 means significant, while the P. Value more than 0.05 is not significant **Conclusion**: Remifentanil produced a fall in B.P. and H. R . so the use of premedication Atropine decrease the incidence of bradycardia and hypotension in pediatric.

Keywords: Bradycardia; Remifentanil; Hypnotics; Sedatives; Analgesics; and Opioid.

INTRODUCTION

The cardiac output in children is rate-dependent, and bradycardia is to be avoided. Blood pressure is a vital physiological index in pediatrics as it gives the perfusion pressure as well as a good indication of blood volume. Invasive procedures such as bone marrow aspiration in children is painful [Morgan, G.E. *et al*., 2004; Birch, B.R.P. *et al*., 1990]. The hemodynamic changes in Remifentanil with or without atropine by using non-invasive blood pressure and heart rate monitoring in pediatric haemato-oncological patients for bone marrow aspiration and biopsy [Morgan, G.E. *et al*., 2002]. Surgery in which the patient presents to the hospital and returns home on the day of the operation. Increasingly performed as for outpatient has many advantages over traditional in-patient surgery. Bone marrow is the active tissue inside our bones which is responsible for the production of blood cells [White, P.F. *et al*., 2005]. Red blood cells for oxygen transport, platelets for bleeding control, and white blood cells for body defense and immunity; the number of conditions like blood diseases, cancers, infections, dysfunction of the immune system, metabolic disorders, and adverse effects of drugs or irradiation can affect the normal function in characteristics of bone marrow. Remifentanil Hydrochloride is a short-acting synthetic opiod of the phenylpiperidine class 2000 times more potent than morphine, widely used in adult general anesthesia, and has been used in pediatric anesthesia. Preliminary pharmacokinetic study in children aged 0-18 years suggested a pharmacokinetic profile similar to that of adults [Demiraran, Y. *et al*., 2017; Fassoulaki, A. *et al*., 2010]. A small volume of distribution, a rapid distribution phase, a half-life with a mean of 3.4 - 5.7 minutes, and extremely rapid elimination. Remifentanil is known to cause bradycardia and hypotension [Bhananker, S.M. *et al*., 2006]. Remifentanil is a potent, short-acting synthetic opioid analgesic drug; a small molecule is given to patients during surgery to relieve pain and as an adjunct to an anesthetic. Remifentanil is a specific mu-type-opioid receptor agonist. Hence, it causes a reduction in sympathetic nervous system tone, respiratory depression, and analgesia. The chemical formula ($C_{20}H_{28}N_2O_5$) [Mantz, J. *et al*., 2011]. Indication for use during the induction and maintenance of general anesthesia. The analgesic effects of Remifentanil are rapid in onset and offset. Its effects and side effects are dose-dependent and similar to other opioids. It has a rapid blood-brain equilibration half-time of 1 ± 1 minute's mean ± SD and a rapid onset of action.

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Remifentanil is a μ-opioid agonist (inhibits the release of neurotransmitter release by reducing Ca^{++} ion current and increase k^{+} ion conductance receptor β-endorphin) with rapid onset and peak effect and short duration of action [Su, F. *et al*., 2011]. The μ-opioid activity of Remifentanil as antagonized by opioid antagonists such as naloxone [Shukry, M. *et al*., 2010]. Atropine binds and inhibits muscarinic acetylcholine receptors, producing a wide range of anticholinergic effects. Atropine is rapidly and well absorbed after intramuscular administration. Atropine disappears rapidly from the blood and is distributed throughout the various body tissues and fluids [Kishi, Y. *et al*., 2010]. Atropine is administrated intravenously or intramuscularly in a range of 0.01 -0.02 mg/kg. Large intravenous doses of up to 3 mg may be required to block the cardiac vagal nerves in treating severe bradycardia [Mashour, G.A. *et al*., 2005; Heinke, W. *et al*., 2005].

PATIENTS AND METHODS

This is a prospective randomized, double-blind study conducted during the 3st of October 2020 to the 23 Th. of February 2021 at the department of anesthesia, nursing home hospital Baghdad medical city complex, Baghdad, Iraq. Eighty patients undergoing diagnostic B.M.A. all of them were with ASA I and II classification. They were 43 males and 37 females.

Inclusion Criteria for Both Gender

1. age: between (3-12) years
2. weight between (8-30) kg
3. ASA: class I and II

Exclusion Criteria

1. ASA class III and IV
2. Patient allergy for any drug use in this study
3. Patient with cardiac disease
4. Patient on any drug affecting CVS

The Statistical Analysis System- SAS (2010) was used to effect of difference factors (group, Base, Age, Gender & weight) in study parameters (HR, S.B.P., and D& M). The least significant difference (LSD) test at the comparative between means in this study. The usual methods, which used in order to analysis and assess the results, they include Descriptive statistics: a- Statistical tables. b- Graphic presentation. Demographic Data of all children (age, gender, weight, ASA) and (H. R.), (B. P.: S. D. M.) were collected using a pre–constructed English language sheet .all children were prepared properly to the procedure. All the procedures of BMA are done between 8 AM to the 1 PM, with a duration of each procedure (anesthesia, BMA, recovery, to the time of discharged) was about 20 min. The children keep fasting for 6 hr for solid food, four hr. for milk, and water for two hr. the Patients were divided to two groups randomly (40 Patients each). All patients were anaesthetized with midazolam 0.05 mg/kg after insertion of a venous catheter, and group A received an intravenous Atropine of o.o1 mg/kg. Group N was received an intravenous normal saline. Also, each patient received a thiopental sleeping dose of 3-6 mg/kg. Both groups received a bolus of Remifentanil 1 μg/kg. in syringe pump 50 ml (dilution =0.5 mg in 500 ml glucose water so each ml =1 μg) for 30 sc. Followed by infusion. in arate 0.01 μg/kg /min till the procedure end; most procedures of B.M.A. lasted < 4 min. all patients were monitored and observed carefully (H.R., non-invasive blood pressure systole, diastole, and the mean blood pressure).using an automated B.P. cuff with an appropriate cuff size in relation to the size of child's arm At the specific time: at time of induction before Remifentanil given, at time of Remifentanil given, T. 3, at recovery (T. 6, T. 9, T. 12, T. 15) to the time of discharged.

RESULTS

The 80 pediatric patients were undergone diagnostic bone marrow aspiration and were divided into two groups, with 40 in each group (A) and group (N). The statistical analysis is showing in Tables and Figures. (Table. 1) and (Figure. 1) shows the relation of the two groups and the mean according to the age group. The values are NS which a P-value (of 0.882, 1.00,0.795) respectively, for (less than 5, 5-10, and more than ten years).

Table 1: No. And mean according to age group.

Age group (year)	Normal saline		Atropine		P-value
	No.	Mean ± SE	No.	Mean ± SE	
Less than 5	14	3.02 ± 0.04	15	3.14 ± 0.04	0.882 NS
5-10	15	7.92 ± 0.09	15	7.92 ± 0.09	1.00 NS
More than ten years	11	13.52 ± 0.67	10	13.47 ± 0.55	0.795 NS
NS: Non-significant.					

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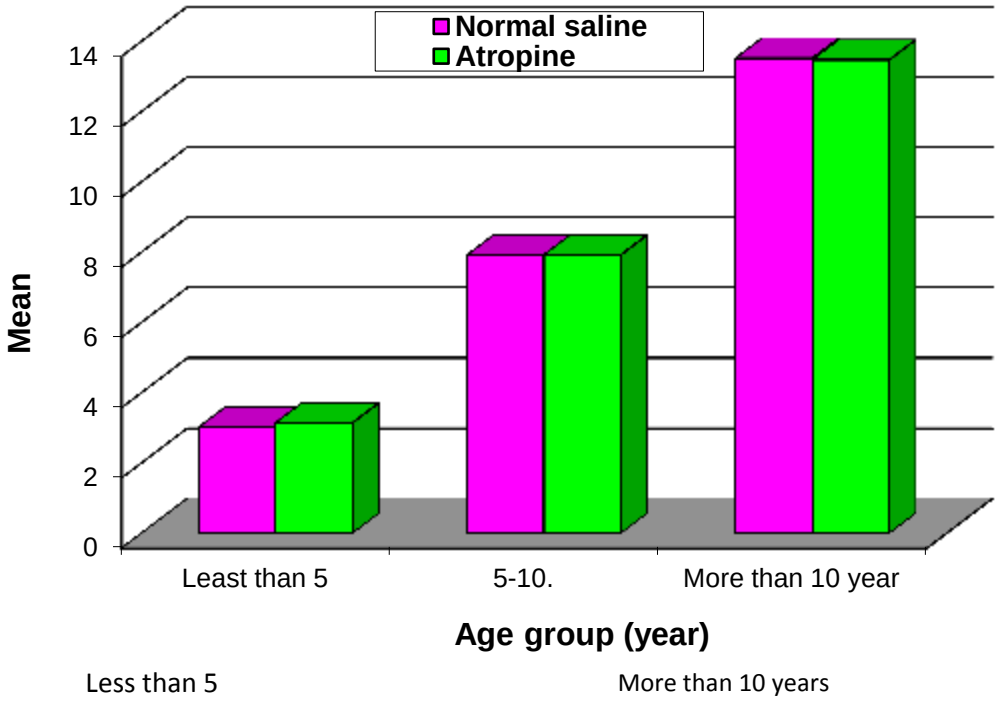

Figure 1: No. And mean according to age group

(Table. 2) and (Figure. 2) shows NS between two groups for a number of means according to weight group P. values for (less than 15,16-20, more than 20 kg.) (0.955, 0.764,0.905) respectively.

Table 2: No. And mean according to weight group

Weight group (Kg.)	Normal saline		Atropine		P- value
	No.	Mean ± SE	No.	Mean ± SE	
Less than 15	8	8.38 ± 0.75	15	8.09 ± 0.69	0.955 NS
16-20	13	18.34 ± 0.92	22	17.97 ± 0.84	0.764 NS
More than 20 kg.	19	26.14 ± 1.04	3	26.42 ± 1.27	0.905 NS
NS: Non-significant					

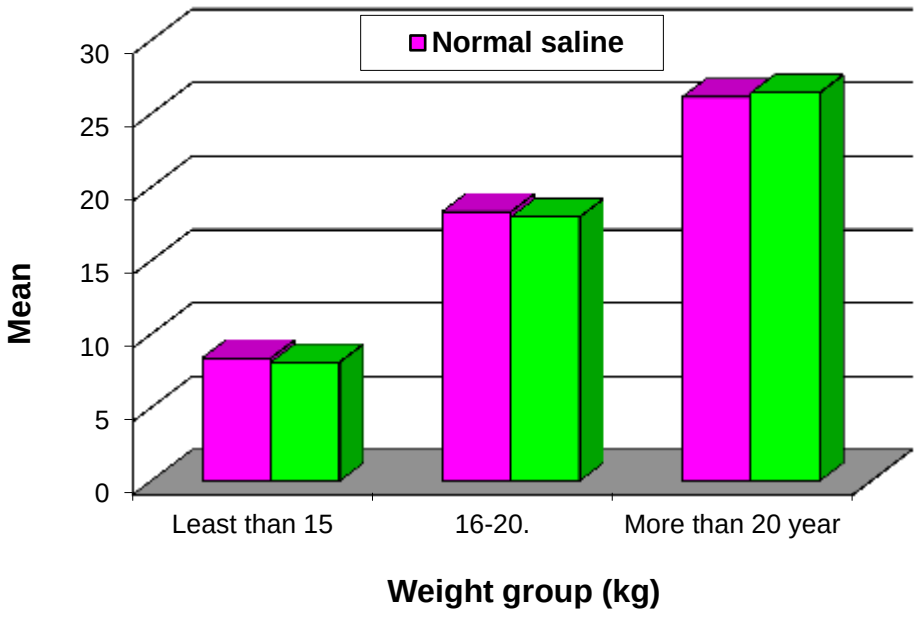

Figure 2: Mean according to body weight group

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(Table. 3) and (Figure 3). The number and percentage according to gender for both normal saline and Atropine groups are not significant. The P. Value for males and females are (47.00 and 57.00) respectively.

Table 3: No. and percentage according to gender

Gender	Normal saline		Atropine	
	No.	%	No.	%
Male	22	53.00	21	47.00
Female	17	43.00	20	57.00
P- value: 0.776 NS NS: Non-significant.				

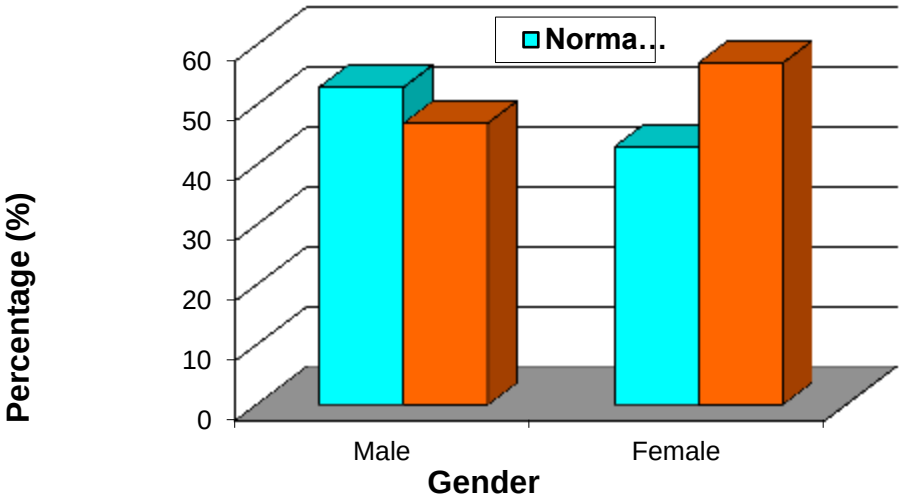

Figure 3: Percentage according to gender

The Table (4) shows the effect of Normal saline and Atropine with Remifentanil on H. R. The statistical analysis shows there is no significant differences between group N and group A before remifentanil was given and at the time of remifentanil given the P. values are 0.39 and 0.31 respectively, but there are significant differences between two groups after three min.(T.3), P. value is 0.047 .while at recovery time (T.6, T.9, T.12, T.15) with a time of discharge are highly significant differences P .values are (0.0003, 0.0004, 0.002 , 0.005 , 0.002) respectively.

Table 4: Comparison between normal saline and atropine group with different bases in HR

Base	Mean ± SD		LSD value	P- value
	Normal saline	Atropine		
At induction before Remifentanil given	117.73 ± 8.93	121.05 ± 12.57	7.74 NS	0.395
At time of Remifentanil given	106.63 ± 12.58	110.30 ± 9.39	7.21 NS	0.313
After 3 min. T 3	99.63 ± 9.04	108.88 ± 9.51	7.78 S	0.047
At recovery T 6	91.80 ± 4.44	114.90 ± 2.59	10.819 **	0.0003
At recovery T 9	97.50 ± 4.18	120.00 ± 2.94	10.759 **	0.0004
At recovery T 12	98.40 ± 5.49	121.30 ± 3.31	13.479**	0.002
At recovery T 15	100.00 ± 5.77	122.10 ± 3.91	14.66 **	0.005
At the time of discharge	114.25 ± 8.74	128.28 ± 13.65	7.92 **	0.002
** (P<0.01), NS: Non-significant.				

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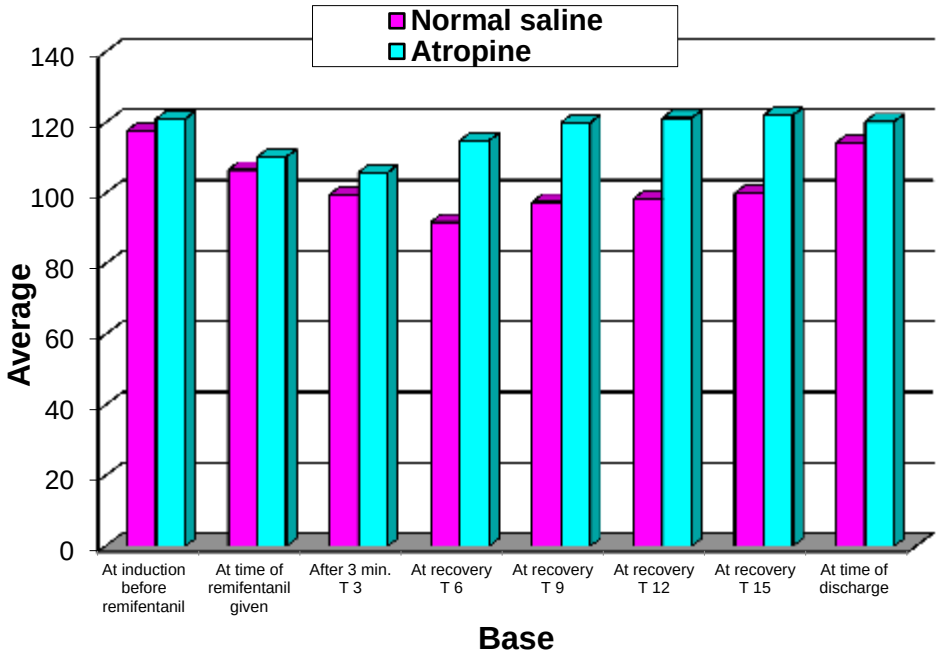

Figure 4: Comparison between normal saline and atropine groups with different bases in HR

Table 5: Comparison between normal saline and atropine group with different bases in S.B.P

Base	Mean ± SD		LSD value	P- value
	Normal saline	Atropine		
At induction before remifentanil given	127.53 ± 11.27	128.98 ± 8.63	6.56 NS	0.661
At time of remifentanil given	116.03 ± 9.53	117.81 ± 12.05	5.91 NS	0.548
After three minutes (T3)	101.65 ± 7.84	114.14 ± 9.65	5.35 S	0.028
At recovery T 6	110.30 ± 3.34	119.40 ± 4.88	8.43 S	0.037
At recovery T 9	110.70 ± 2.54	121.50 ± 4.14	10.21 S	0.029
At recovery T 12	115.80 ± 2.68	129.30 ± 3.63	9.63S	0.045
At recovery T 15	121.80 ± 2.92	132.30 ± 3.64	7.79S	0.049
At the time of discharge	125.05 ± 9.77	138.21 ± 5.41	4.32 S	0.043
** (P<0.01), NS: Non-significant.				

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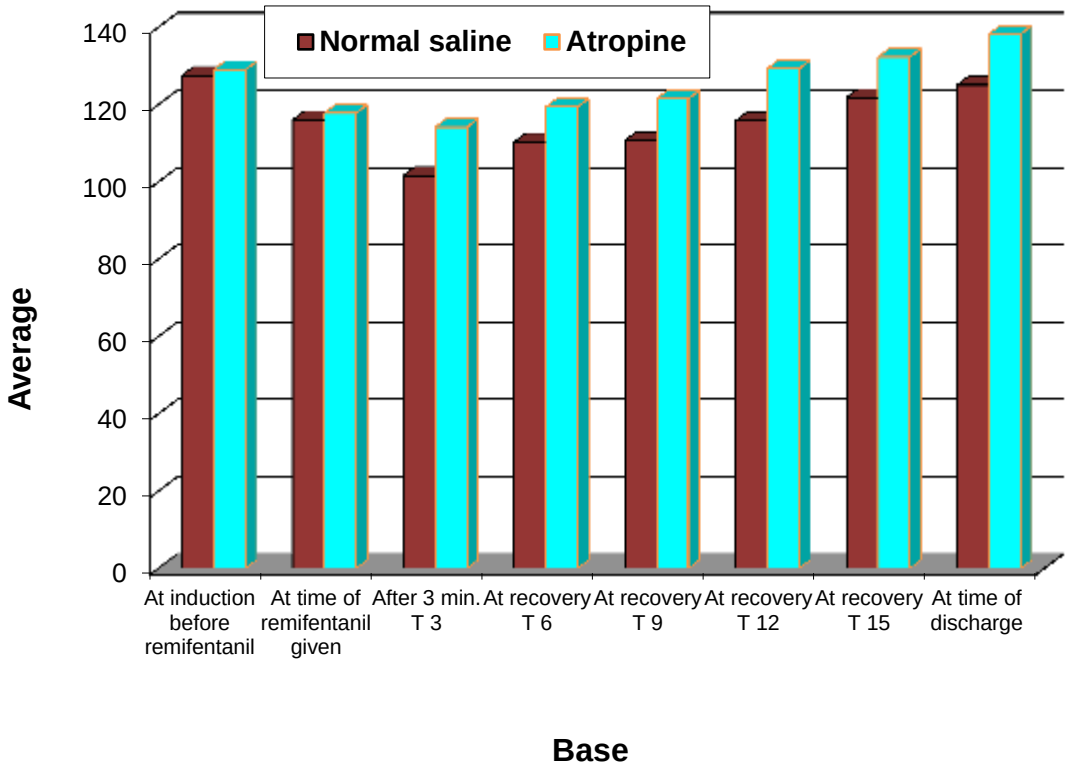

Figure 5: Comparison between normal saline and atropine group with different bases in S.B.P

Table 6: Comparison between normal saline and atropine group with different bases in D.B.P

Base	Mean ± SD		LSD value	P- value
	Normal saline	Atropine		
At induction before remifentanil given	71.77 ± 5.63	79.54 ± 9.26	5.39 **	0.0054
At time of remifentanil given	63.73 ± 5.68	66.65 ± 8.25	5.33 NS	0.278
After three minutes (T3)	60.33 ± 6.48	61.21 ± 8.52	4.87 NS	0.962
At recovery T 6	68.10 ± 2.13	71.30 ± 3.93	9.398 NS	0.539
At recovery T 9	70.10 ± 1.36	72.00 ± 2.14	5.346 NS	0.420
At recovery T 12	71.50 ± 1.75	72.50 ± 2.06	5.70 NS	0.716
At recovery T 15	72.60± 1.52	75.30 ± 2.08	5.42 NS	0.309
At the time of discharge	75.15 ± 8.21	77.68 ± 6.95	4.64 NS	0.245
** (P<0.01), NS: Non-significant.				

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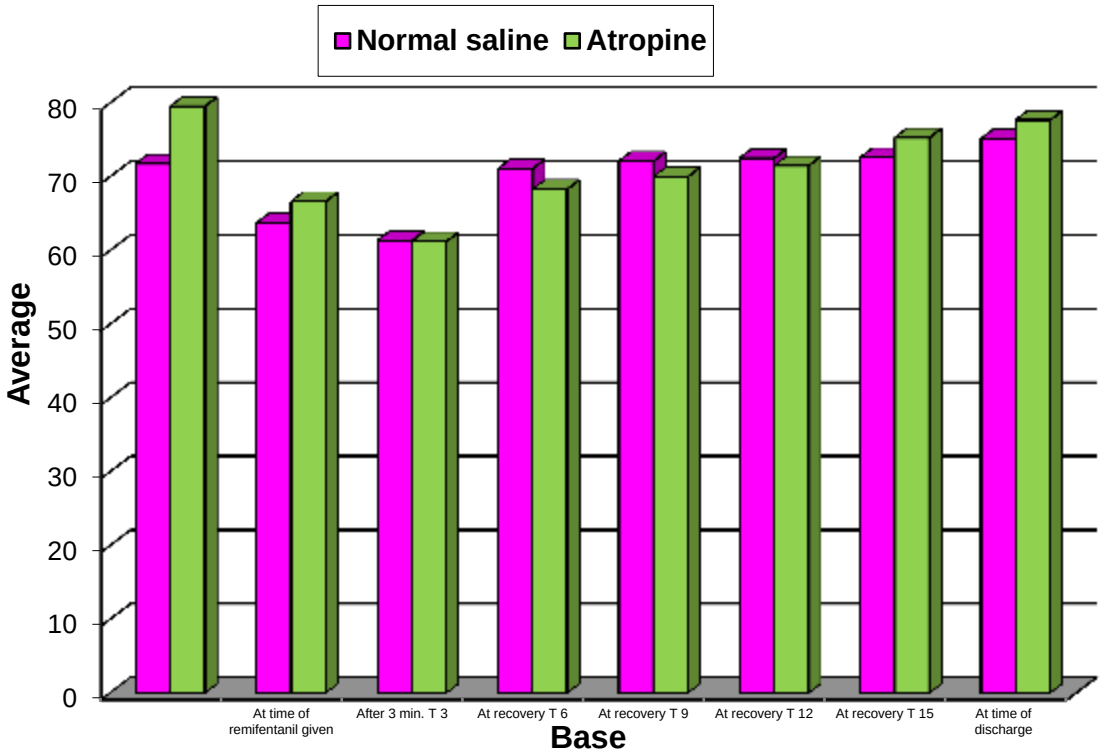

Figure 6: Comparison between normal saline and atropine group with different bases in D.B.P

Table 7: Comparison between normal saline and atropine groups with different bases in M.B.P

Base	Mean ± SD		LSD value	P- value
	Normal saline	Atropine		
At induction before remifentanil given	93.30 ± 8.63	98.44 ± 11.04	5.19 NS	0.062
At time of remifentanil given	82.05 ± 7.35	86.74 ± 5.92	4.48 NS	0.105
After three minutes (T3)	73.33 ± 8.54	78.65 ± 11.39	4.39 *S	0.025
At recovery T 6	82.00 ± 1.22	87.10 ± 3.12	7.041 *S	0.05
At recovery T 9	83.20 ± 0.81	88.70 ± 2.82	4.184 *S	0.038
At recovery T 12	85.40 ± 2.00	91.40 ± 2.47	4.33 **	0.0119
At recovery T 15	93.20 ± 1.61	90.10 ± 3.48	5.06 * S	0.042
At the time of discharge	91.20 ± 11.47	97.79 ± 7.84	3.572 **	0.0058
** (P<0.01), NS: Non-significant.				

DISCUSSION

Many authors have shown that Remifentanil can induce a decrease in heart rate in pediatric patients. According to our data, Remifentanil caused a progressive decrease in heart rate during the first level of infusion at the time of Remifentanil given and then a further reduction during the second level of infusion (T 3) the difference between two groups: group A that pre-treatment with Atropine the level of Bradycardia less than group N that pre-treatment with normal saline and even after the infusion of Remifentanil stopped and all episodes of hypotension and bradycardia resolved spontaneously without pharmacological intervention so heart rate, blood pressure returned to the same level before induction [Hanning, C.D, 2005; Dreher, M. *et al*., 2010]. The degree of H.R. increase was much greater in group A than in group N. That finding goes with research conducted by Chanavaz [Zhang, J. *et al*., 2016] and colleagues when they found a progressive decrease in heart rate during the first level of infusion, which was obviousin control group more than Atropine group in a similar way Tirel [Dorantes Mendez, G. *et al*., 2013] and colleagues found Remifentanil can cause arterial hypotension and a moderate bradycardia, which can be counteracted by the administration of Atropine while Ross and colleagues showed a 17 % incidence of remifentanil –related hypotension,

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indeed Klemola [Ida, M. *et al*., 2014] and colleagues reported a significant fall of 6-9% in heart rate when remifentanil was administrated at induction of anesthesia to children who had been pre-treated with Atropine before induction also reported a decrease in mean blood pressure of 11-13% after anesthetic induction with remifentanil. While Keidan [Juri, T. *et al*., 2014] and colleagues showed the addition of propofol with Remifentanil infusion (TIVA)without the use of Atropine lead to more reduced in H.R. and B.P. with increased risk of respiratory depression because the propofol itself effect on the cardiovascular system lead to hypotension and bradycardia, indeed Wee and colleagues found a higher incidence of hypotension and bradycardia when Remifentanil infusion was given to infants with a one µg /kg/min. Loading dose and an infusion of 0.25 µg/kg/min. And their neonates' patients were known to be sensitive to an inhalational anesthetic agent, which may lead to more decrease in H.R. and B.P. for such major and prolonged operations. [Joo, H.S. *et al*., 2014]

CONCLUSION

Remifentanil is effective in children and can be used safely in B.M.A.; although Remifentanil produced a fall in B.P. and H.R., so it's safe in combination with atropine. This study is recommended to 1) Remifentanil is a potent, synthetic opioid with a short duration of action, so it is suitable for short procedures and day-case surgery. 2) Remifentanil can cause arterial hypotension and bradycardia, so it's recommended to use Atropine to prevent side effects.

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