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Dr. VS Anjankumar MD
Associate Professor of
Pediatrics, Sri Venkateswara
Medical College, Tirupati,
Andhra Pradesh, India

Dr. K Sivaramudu
Assistant Professor,
Department of Pediatrics, Sri
Venkateswara Medical College,
Tirupati, Andhra Pradesh,
India

Dr. I Bhaskar Naik
Assistant Professor,
Department of Pediatrics, Sri
Venkateswara Medical College,
Tirupati, Andhra Pradesh,
India

T Jayachandra Naidu MD
Professor, Department of
Pediatrics, Sri Venkateswara
Medical College Tirupati,
Andhra Pradesh, India

Dr. D Priyanka
Resident, Department of
Pediatrics, Sri Venkateswara
Medical College Tirupati,
Andhra Pradesh, India

S Suchitha
Pharm. D Intern, Department
of Pharmacy Practice, Sri
Padmavathi School of
Pharmacy, Tiruchanoor,
Tirupathi, Andhra Pradesh,
India

Corresponding Author:
Dr. VS Anjankumar MD
Associate Professor of
Pediatrics, Sri Venkateswara
Medical College, Tirupati,
Andhra Pradesh, India

Efficacy of bubble continuous positive airway pressure in newborns with respiratory distress and its outcome in tertiary care hospital, Tirupathi

Dr. VS Anjankumar MD, Dr. K Sivaramudu, Dr. I Bhaskar Naik, T Jayachandra Naidu MD, Dr. D Priyanka and S Suchitha

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Abstract

Background: Respiratory distress is one of the commonest emergency occurring mostly within the first 48-72 hours of life. Bubble continuous positive airway pressure (bCPAP) is essential to manage acute respiratory distress in neonates.

Method: A Hospital based prospective observational study was done at SNCU at Department of Pediatrics, Sri Venkateswara Ramnarayan Ruia Government General Hospital, Tirupati from October 2017 to September 2018. Efficacy of bCPAP was judged based on Downe /SAS scoring.

Results: Out of 171 babies who were managed with bCPAP, it proved effective in 118 babies (69%). The results analyzed based on gender and gestational age were found statistically significant difference ($p < 0.05$) and the results analyzed based on birth weight found no statistically significant difference in the outcome between the two groups ($p > 0.05$). The mean age for initiation of treatment is 9.39 ± 15.022 hours. Overall Mean duration on bCPAP was 24.24 ± 18.22 . The success rate was more in babies with RDS 68.2%. There was a significant improvement in Downe/SAS scores in babies with RDS, Pneumonia, MAS and TTNB. The complications were more in failure group. Study of mortality rate was more in the failure group 81% and the survival rate was more in success group 100%.

Conclusion: CPAP appears to be the best option to manage infants with respiratory distress at SNCUs of peripheral levels.

Keywords: respiratory distress syndrome (RDS), bubble CPAP, Downe score/SAS score, meconium aspiration syndrome (MAS), transient tachypnea of new borns (TTNB)

1. Introduction

India constitutes one fifth of global live births and in neonatal deaths more than a quarter. In 2013, in India nearly 0.75 million neonates died, which was the highest in the world [1]. Respiratory distress is one of the commonest emergency occurring mostly within the first 48-72 hours of life [2]. Respiratory distress in the neonate is diagnosed by tachypnoea or respiratory rate of more than 60/minute, chest indrawings or retractions, noisy respiration in the form of grunt, stridor or wheeze [3]. Respiratory distress severity is assessed by Silverman Anderson Score (SAS) [4] in preterms and with Downe score [5] in late pre terms & term babies. Failure of early recognition and management of respiratory distress leads to short and long-term complications, including BPD, respiratory failure and even death [6]. Respiratory support to manage acute respiratory distress in neonates can be provided by continuous positive airway pressure (CPAP) or mechanical ventilation [7]. CPAP is a non-invasive form of respiratory support which does not require complex technical expertise. CPAP can be applied via a face mask, nasopharyngeal tube, or nasal prongs, using a conventional ventilator, bubble circuit or a CPAP driver. Bubble CPAP (bCPAP) is one of the low cost nasal CPAP delivering systems, with underwater seal. CPAP has been studied extensively in pre terms with respiratory distress syndrome (RDS) or hyaline membrane disease (HMD). But with the benefits of CPAP, a variety of neonatal respiratory conditions can be managed with it alone [8, 9].

2. Objectives

To determine the efficacy of Bubble Continuous Positive Airway Pressure in newborns with respiratory distress in SNCU.

3. Method

A Hospital based prospective observational study was done at SNCU at Department of Pediatrics, Sri Venkateswara Ramnarayan Ruia Government General Hospital, Tirupati from October 2017 to September 2018. All newborns with respiratory distress who were admitted at SNCU at Department of Pediatrics, Sri Venkateswara Ramnarayan Ruia Government General Hospital, Tirupati during the study period were included based on inclusion and exclusion criteria. Permission was obtained from institutional ethics committee, Sri Venkateswara Medical College, Tirupati before starting the study. Baby’s mother or caretaker was explained about the condition and the study in their own language and consent was taken before the newborn was recruited into the study.

3.1. Inclusion criteria

1. In preterm babies with Silverman Anderson score 3 – 6.
2. In term babies with Downe Score 4 – 6.

3.2. Exclusion criteria

1. Neonates with congenital anomalies.
2. Neonates with severe cardiovascular instability
3. Neonates requiring intubation at birth
4. Pneumothorax and other air leaks
5. Parents not willing to give consent

Details of birth history, risk factors in pregnancy, type of delivery, and need for resuscitation were recorded. Newborns were then connected to FISCHER & PAYKEL bubbleCPAP device with HUDSON nasal prongs of appropriate size according to the birth weight.

All babies were nursed under radiant warmers on servo-controlled mode. Orogastric tubes were inserted and connected to open syringes (without piston) for venting. Strict asepsis was observed. Bubble CPAP was started with settings of CPAP - 5 cms of H2O and FiO2 50% and flow rate 5 lit / min. These settings were adjusted accordingly to maintain pulse oximeter saturation between 88 – 94 %. Babies with a diagnosis of RDS were given surfactant if indicated and this was done by INSURE (Intubate, Surfactant Extubate) technique and babies were then put back on bCPAP. Continuous monitoring of respiratory distress by means of SAS/Downe score and oxygen saturation with pulse oximeter was done. All the other vital signs were also taken care of. Time of starting of bCPAP, total duration of therapy are noted. All the collected data while monitoring was documented on monitoring chart for each baby. Neonates were weaned off from bCPAP when there was no respiratory distress or simply if the Downe / SAS scores were 90% with FiO2 requirement 92% were gradually weaned off from the oxygen. Management of other co-morbid conditions such as pulmonary hypertension, shock, seizures, renal dysfunction, therapeutic hypothermia, fluid, electrolyte, acid and base imbalances were at the discretion of the attending physician.

Data was collected in terms of efficacy -Success of bCPAP, gender distribution, gestational age & birth weight distribution, age at initiation of bCPAP, Changes in Downe/SAS score and total duration on CPAP and outcome—Shifting to mechanical ventilation, complications, mortality & survival. After the completion of the study, data was analyzed using appropriate statistical methods to find out the efficacy of bubbleCPAP in the treatment of respiratory distress. 21 Babies treated with bubbleCPAP

were classified into two groups namely success and failure group and comparison of outcome variables between the groups were carried out. Categorical variables were compared with Chi-square test, while continuous variables were analyzed using Student’s t-test for normal distributions. Significance was defined as P < 0.05 for the predefined outcome variables. Analysis was done using SPSS software (version 20.0)

4. Results

Table 1: BCPAP treatment Efficacy (success /failure) among babies

Total No. of babies Treated	Success		Failure	
	Number	Percentage	Number	Percentage
171	118	69%	53	31%

The table shows the efficacy in study group of the CPAP. Among 171 babies, 118 improved with success rate of 69%, whereas 53 babies (31%) failed requiring higher mode of ventilation.

Table 2: Gender wise distribution of the study group

Gender	Total	Success		Failure	
		No.	Percentage	No.	Percentage
Male	106	78	73.5%	28	26.5%
Female	65	40	61.5%	25	38.5%
Total	171	118		53	

p-Value 0.0001

Above tables shows that among 171 babies, 106 were males & 65 were female babies. In males, 73.5% were in success group and 26.5% were in failure group. In females, 61.5% were in success with 38.5% in failure group.

Table 3: Gestational age wise Distribution of babies and results

Gestational Age(weeks)	Total	Success		Failure	
		No.	Percentage	No.	Percentage
28-30	35	14	40%	21	60%
31-32	34	27	79.5%	7	20.5%
33-34	46	34	74%	12	26%
35-36	18	16	88.8%	2	11.2%
37-38	22	18	81.8%	4	18.2%
>38	16	9	56.25%	7	43.75%
Total	171	118		53	

p-Value 0.006

Success rate in 28-30 weeks was 40%, in 31-32 weeks it was 79.5%, in 33-34 weeks 74%, among 35-36 weeks 88.8%, in 37-38% it was 81.8% and in >38 weeks of gestational age 56.25%. p-Value was 0.006. Mean gestational age in the study was 33.63±3.345.

Table 4: Efficacy and Distribution of babies based on birth weight

Birth Weight Gms	Total	Success		Failure	
		No.	Percentage	No.	Percentage
<999	9	3	33.3%	6	66.7%
1000-1500	75	46	61.4%	29	38.6%
1501-2000	42	35	83.4%	7	16.6%
2001-2500	19	14	73.7%	5	26.3%
2501-3000	20	15	75%	5	25%
>3000	6	5	83.3%	1	16.7%
Total	171	118		53	

p-Value 0.7

In <999 gms, success rate was 33.3% and failure 66.7%. In 1000-1500 gms, success rate was 61.4% & failure rate 38.6%. In 1501-2000gms success rate was 83.4% with a failure rate 16.6%. The success & failure rates in 2001-2500 gms were 73.7% & 26.3%. In 2501-3000 gms, 75% was the success rate and 25% was the failure rate. There was a success rate of 83.3% & failure rate of 16.7% in >3000gms. In our study mean birth weight was 1.7242 ±0.62345.

Table 5: Distribution based on Indications for starting bCPAP

Indication	Total	Success		Failure	
		No.	Percentage	No.	Percentage
RDS	113	77	68.2%	36	31.8%
Pneumonia	31	20	64.6%	11	35.4%
MAS	17	11	64.7%	6	35.3%
TTNB	10	10	100%	0	0%

p-Value 0.0001

It was observed that success rate in babies with RDS was 68.2% & failure rate was 31.8%. In babies with Pneumonia, success & failure rates were 64.6% and 35.4%. Success and failure rates in MAS were found to be 64.7% & 35.3%. In TTNB there was 100% success rate.

Table 6: Distribution of mean age at the time of initiation of treatment

No. of babies	Mean age ± SD (hours)	Range (hours)
171	9.39±15.022	1-120

Table 8: Downe / SAS score in study group before and after CPAP

Downe's/SAS Score	At Start DS		After 6hrs		After 12hrs	
	No.	Percentage	No.	Percentage	No.	Percentage
<4	0	0%	35	20.5%	88	51.5%
4	68	39.7%	75	43.9%	36	21.0%
5	61	35.6%	36	21.0%	25	14.7%
6	42	24.5%	25	14.6%	19	11.11%
7	0	0%	0	0%	3	1.75%
Total	171		171		171	

Table shows distribution of babies based on Downe / SAS score. 68 (39.7%) were in score 4, 61(35.6%) were in score 5, 42(24.5%) were in score 6 before institution of CPAP. After 6hrs of bCPAP, there were 20.5 % of babies with score <4, 43.9% of babies with score 4, 21.6% with score 5 and 14.6% were in score 6. After 12 hrs of bCPAP support, 51.5% were in <4 score, 21% in score 4, there were 14.7% babies in score 5, with 11.11% babies in score of 6 and score 7 was present in 1.75% babies. The mean DS at start

The mean age for initiation of treatment is 9.39±15.022 hours with range of 1-120 hours.

Group	Number	Mean± SD	Range (hours)
Success	118	8.74±15.373	1-120
Failure	53	10.85±14.246	1- 84

p-Value 0.152

Mean age in success group was 8.74±15.373 and that of failure group was 10.85±14.246.

Table 7: Mean Duration of Treatment in Success and Failure Groups

No. of babies	Mean duration ± SD (hours)	Range (hours)
171	24.24±18.22.	7-96

Group	Number	Mean± SD	Range (hours)
Success	118	24.42±17.726	7-96
Failure	53	23.83±19.451	12-86

p-Value 0.09

Tables shows analysis of the duration of treatment in success and failure groups. The mean duration in success group was 24.42±17.726 hours with range of 7- 96 hours. Similarly mean duration of treatment in failure group was 23.83±19.451 hours range being 12- 86 hours. Mean duration is 24.24±18.22.

Table 9: Response to Bubble CPAP in studied babies (n=171)

	Score	Success(118)		Failure(53)		Total	p- Value
		No.	Percentage	No.	Percentage		
At start	4	50	73.5%	18	26.5	68	0.55
	5	41	67.2%	20	32.8%	61	
	6	27	64.3%	15	35.7%	42	
6Hrs	<4	35	100%	0	-	35	0.001
	4	63	84%	12	16%	75	
	5	16	44.4%	20	55.6%	36	
	6	4	16%	21	84%	25	
12Hrs	<4	88	100%	0	-	88	0.001
	4	24	66.6%	12	33.4%	36	
	5	5	20%	20	80%	25	
	6	0	-	19	100%	19	
	7	0	-	3	100%	3	

of bCPAP was 4.85±0.79, mean DS after 6hrs of CPAP therapy was 4.30±0.957 and mean DS after 12 hrs was 3.83±1.192. Out of 171 babies, bubble CPAP was successful in 69% (118) of babies. The response to bCPAP in studied babies is shown. In the success group, 42.4%, 34.7% and 22.9% of the babies had DS of 4, 5 and 6 respectively at the start of CPAP therapy. In the failure group 34%, 37.7% & 28.3% of the babies had DS of 4, 5 and 6 respectively at the start of CPAP therapy.

Table 10: Distribution according to Downe scores at 6 and 12 hours in studied babies with initial score of 4

Downes Score	6Hrs		12Hrs	
	Success(50)	Failure(18)	Success(50)	Failure(18)
<4	21(42%)	0(0%)	44(88%)	0(0%)
4	25(50%)	3(16.7%)	5(10%)	1(5.6%)
5	4(8%)	10(55.6)	1(2%)	10(55.6%)
6	0%	5(27.7%)	0%	7(38.9%)

p-Value <0.05 p-Value <0.05

In the success group, 42% and 88% of babies who had a DS of 4 at the start of CPAP therapy improved to a score of <4 at 6 hours and 12 hours of CPAP therapy respectively. This was found out to be statistically significant.

Table 11: Distribution according to Downe score at 6 and 12 hours in babies with initial score of 5

Downes Score	6Hrs		12Hrs	
	Success(41)	Failure(20)	Success(41)	Failure(20)
<4	14(34.2%)	0(0%)	28(68.3%)	0(0%)
4	20(48.8%)	7(35%)	11(26.8%)	8(40%)
5	7(17%)	2(10%)	2(4.9%)	3(15%)
6	0%	11(55%)	0%	8(40%)
7	0	0	0	1(5%)

p-Value<0.005 p-Value<0.05

Among the babies having an initial score of 5, 34.2% and 68.3% showed improvement to a score of <4 at 6 hours and 12 hours of CPAP therapy.

Table 12: Distribution according to Downe score at 6 and 12 hours in babies with initial score of 6

Downes Score	6Hrs		12Hrs	
	Success(27)	Failure(15)	Success(27)	Failure(15)
<4	0%	0(0%)	16(59.3%)	0(0%)
4	18(66.60%)	2(13.3%)	8(29.60%)	3(20%)
5	5(18.50%)	8(53.3%)	2(7.40%)	7(46.7%)
6	4(14.80%)	5(33.3%)	1(3.70%)	3(20%)
7	0	0	0	2(13.3%)

p-Value 0.0004

Among the babies having an initial score of 6, 0% and 59.3% of the babies improved to a score <4 at 6 hours and 12 hours of bCPAP therapy.

Table 13: Distribution according to SAS score at 6 and 12 hours in babies with RDS

SAS score	6hrs		12 hrs	
	Success(77)	Failure(36)	Success(77)	Failure(36)
<4	23(30%)	0	55(72%)	0
4	43(56%)	8	17(22%)	6
5	8(10%)	15	4(5%)	16
6	3(4%)	13	1(1%)	12
7	0	0	0	2

p-Value <0.05 p-Value <0.05

Significant reduction in SAS score was observed after 6hrs

Table 18: Study of complications and morbidity in success and failure

Complications	Total	Success(118)		Failure(53)	
		No.	Percentage	No.	Percentage
ROP	7	7	6%	0	0
Recurrent Apnoea	15	9	7.6%	6	11.3%
Shock	20	0	0	20	37.8%

& 12 hrs of bCPAP therapy in babies with RDS.

Table 14: Distribution according to Downe /SAS score at 6 and 12 hours in babies with Pneumonia

Downe/SAS Score	6hrs		12 hrs	
	Success(20)	Failure(11)	Success(20)	Failure(11)
<4	6	0	16	0
4	10	3	4	4
5	4	3	0	2
6	0	5	0	4
7	0	0	0	1

p-Value <0.05 p-Value <0.05

In babies with Pneumonia, Downe / SAS score reduced significantly after 6hrs & 12 hrs of bCPAP therapy.

Table 15: Distribution according to Downe score at 6 and 12 hours in babies with MAS

Downe Score	6hrs		12 hrs	
	Success(11)	Failure(6)	Success(11)	Failure(6)
<4	3	0	8	0
4	5	1	2	2
5	2	2	1	2
6	1	3	0	2
7	0	0	0	0

p-Value <0.05 p-Value <0.05

Downe score reduced in babies with MAS after 6hrs & 12 hrs of bCPAP therapy. Statistically significant difference.

Table 16: Distribution according to Downe score at 6 and 12 hours in babies with TTNB

Downe/SAS score	6hrs	12hrs
	Success(10)	Success(10)
<4	3	9
4	5	1
5	2	0
6	0	0
7	0	0

Here also Downe score decreased with bCPAP therapy. In the failure group, none of the babies had a score of 4 at the start of bCPAP therapy. None of the babies having initial score of 5 improved to a score <4. Among the babies who had initial score of 6, none of the babies had decrease in score at 6 hours and 12.5% of the babies improved to a score of 5 at 12 hours of bCPAP therapy.

Table 17: Shifting to mechanical ventilation

Mechanical ventilation	Success(118)	Failure(53)	Total
	0	53(100%)	53

From the above table shifting to mechanical ventilation from the failure group was 100% compared to success group.

Pulmonary Hemorrhage	17	0	0	17	32%
BPD	6	2	1.7%	4	7.5%
Nasal septum injury	20	18(15.3%)	2(3.7%)	-	-
	Success(118)	Failure(53)	p-Value		
Complications	36(30.5%)	49(92.5%)	0.0002		

Compared to failure and success group, complications were more in failure group. p-value <0.05, highly significant.

Table 19: Study of mortality in success and failure group

	Success	Failure	p-Value
Total	118	53	<0.05
Mortality	0	43(81%)	

From the above table, mortality rate in the failure group was 81% compared to success group. P-value is <0.05 significant.

Table 20: Study of Survival in success and failure group

	Success	Failure	p-Value
Total	118	53	<0.05
Survival	118(100%)	10 (20%)	

From the above table, survival rates in success and failure groups were 100% and 19% respectively. P-value is <0.05 significant. The overall survival rate in the study was came out to be 75%.

5. Discussion

This study was a prospective observational study of the neonates with Respiratory distress. The neonates were clinically evaluated and to find out the cause for respiratory distress laboratory investigations were done. Out of 171 babies, 118 babies (69%) were effectively managed with bubble CPAP. Remaining 53 babies had to be intubated and required more invasive mechanical ventilation. The success rate in Singh *et al.* [10] study was 54.7%, Sethi *et al.* [11] study was 60% and Koti *et al.* [12] 75% was observed.

5.1. Gender

In the present study the success rates in males and females were 73.50% and 61.50%. Parasuramappa *et al.* study [13] showed a success rate of 61.5% in males & 38.5% in females. In Singh *et al.*, [10] success rates were 55.6% & 4.4% in males and females respectively. In both the studies there was no statistically significant difference in outcome between the two groups, which was found to be similar to Koti *et al.* [12] and Urs *et al.* [14] studies. But Sandri F *et al.* [15] study has shown increased need for respiratory support in male infants.

5.2. Gestational age

Present study shows better outcome in 35 - 38 weeks of gestation i.e., 85% success rate. A statistically significant association was found between bubble CPAP success and gestational age. Similar significant association was found with 32-34 weeks in Parasuramappa *et al.* study [13]. This was similar to the findings in Urs *et al.* [14]. In Singh *et al.* study [10] ≤ 30 weeks of gestational age had significant effect on CPAP success which was found similar to the study by Ammari *et al.* [16]. Higher gestational age had a significantly positive effect on the success of bCPAP similar to the study by Hameed *et al.* [17]. This might be because that indication

for starting bCPAP was different. The mean gestational age of the babies was 33.626 ± 3.3449 weeks in the present study.

5.3. Birth weight

In the present study it was observed that there was no significant difference in the outcome of babies based on birth weight (p-value >0.05). Urs *et al.* [14] have shown better outcome in babies with birth weight 1000-1500 gm (p<0.001). In this study mean birth weight was 1.7515 ± 0.62482 . From this study, observation that with increase in birth weight, bCPAP success rate has increased except for babies in the range of 2000- 3000gms which was found out to be similar to Singh *et al.* [10] but the exception group was babies with weight ≥ 2500 gms. Probable explanation might be that MAS and pneumonia being the cause of respiratory distress in most of the babies of this weight category. It was noticed in the study that the gender and mean gestational age had impact on the success of bCPAP which was different from that of the study conducted by Sethi *et al.* [11].

5.4. Indications

Success rates in the present study in RDS was 68.2%, in Pneumonia 64.6%, in MAS it was 64.7% and in TTNB the success rate was 100%. In Bajad *et al.* study [19] success rate in RDS was 64.5%, in Pneumonia 82%, it was 86% in MAS and in TTNB group success rate was 100%.

5.5. Age of initiation

The mean age for initiation of treatment was 9.39 ± 15.022 hours with range of 1-120 hours. Mean age in success group was 8.74 ± 15.373 and that of failure group was 10.85 ± 14.246 . There was no difference in the result with the age of initiation of bCPAP in our study. p-Value 0.15. It might be due the broad range of age at the time of initiation of bCPAP. In Sethi *et al.* [11] study found that the age of neonate at which CPAP had been applied median = 2 (0.3-6) hours of life was a significant contributor for the CPAP failure (P=0.024) which is different from that found by Koti *et al.* [12] (P value =0.58).

5.6. Duration

The mean duration on bCPAP in the present study was 24.24 ± 18.22 hours. In success group, it was 24.42 ± 17.72 hours & that of failure group 23.83 ± 19.451 hours. p-Value 0.09. Singh *et al.*, [10] the mean duration on CPAP was 2.45 ± 1.27 days, similar reported by Umran *et al.* [18] 2.85 (days) ± 2.11 , but different with Koti *et al.*, [12] that was 0.97 days. In Sethi *et al.* [11] study the duration of stay on CPAP was more in success group.

5.7. Downe/SAS Score

In this present study of bCPAP, efficacy was judged based on Downes / SAS scoring. In the success group, 42.4%, 34.7% and 22.9% of the babies had DS of 4, 5 and 6 respectively at the start of CPAP therapy. In a study conducted by Parasuramappa *et al.* [13] in the success group,

12.1%, 51.6% and 36.3% of the babies had DS of 4, 5 and 6 respectively at the start of CPAP therapy.

Among the babies having an initial score of 5, 63.8% and 95.8% showed statistically significant improvement to a score of <4 at 6 hours and 12 hours of CPAP therapy. Among the babies having an initial score of 6, 57.6% and 75.8% of the babies improved to a score <4 at 6 hours and 12 hours of CPAP therapy which was statistically significant. Urs *et al.* [14] have also shown significant improvement in Downe score after application of bubble CPAP. It was found that there was significant reduction in Downe / SAS scores after 6hrs & 12 hrs of bCPAP irrespective of the indication for which bCPAP has been started. There was improvement of scores in all the groups i.e., RDS, Pneumonia, MAS & TTNB with bCPAP.

5.8. Shifting to mechanical ventilation

In the present study shifting to mechanical ventilation from the study group was 31% compared to Koti *et al.* [12] where it was 25%.

5.9. Complications and morbidity

Compared to failure and success group, complications were more seen in failure group. In the present study, 6% had ROP, Recurrent apnoea was seen in 7.6%, BPD 7.5% and 3.7% had nasal septum injury in success group. In the failure group 37.8% had Shock and pulmonary hemorrhage was present in 32%. Compared to Koti *et al.*, [12] 5% babies developed retinopathy of prematurity, apnoea was present in 14.3% in success group and in failure group 14% developed shock and apnea in 28.6%.

5.10. Mortality

In the present study, mortality rate in the failure group was 81% compared to success group p-value is <0.05 significant. Koti *et al.* [12] study showed 2.4% of mortality in success group and 35.7% in failure group.

5.11. Survival

Overall survival rate in the study was found to be 75%. Survival rate in success group was 100% and in failure group it was 20%. In Iqbal *et al.* study, [20] survival rate in success group was 97% and in failure group it was 61%.

6. Conclusion

BCPAP was found to be safe, inexpensive and effective means of respiratory support in respiratory distress of any cause and is an effective way of improving oxygenation and can reduce the need for mechanical ventilation. It is effective in both term & preterm babies with varied respiratory conditions. Use of a bCPAP system to treat neonatal respiratory distress resulted in 75% absolute improvement in survival. BCPAP can be used as first line respiratory support between nasal oxygen and mechanical ventilation. Starting early bCPAP in neonates with MAS and pneumonia reduces the subsequent need for MV. Both short & long term complications can be reduced with the use of bCPAP. CPAP appears to be the best option to manage infants with respiratory distress at SNCUs of peripheral levels and to prevent up-transfers to already overburdened Level III / tertiary care centres.

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