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# Comparative Efficacy of Nebulized 3% Hypertonic Saline Versus 0.9% Normal Saline in Children with Acute Bronchiolitis: A Randomized Clinical Trial

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**Abstract:** ***In this randomized clinical trial, we compared the efficacy of nebulized 3 hypertonic saline versus normal saline in children aged 3 to 24 months diagnosed with acute bronchiolitis. Our findings suggest that while both treatments are safe, 3 hypertonic saline may offer benefits in reducing hospital stay duration without significantly affecting clinical severity or the need for additional nebulizations. Further research is necessary to confirm these outcomes and explore potential mechanisms.***

**Keywords:** acute bronchiolitis, hypertonic saline, nebulization, pediatric respiratory diseases, randomized clinical trial

**Background**
This study's significance lies in addressing the clinical question of whether 3 hypertonic saline is superior to normal saline in managing acute bronchiolitis in children, potentially influencing pediatric treatment protocols and improving patient outcomes

## 1. Introduction

The hallmark of management for children with bronchiolitis is symptomatic care. All infants and children who are diagnosed with bronchiolitis should be carefully assessed for adequacy of hydration, respiratory distress, and presence of hypoxia.

Children who present with mild to moderate symptoms can be treated with interventions like nasal saline, antipyretics, and a cool-mist humidifier. Those children with severe symptoms of acute respiratory distress, signs of hypoxia, and/or dehydration should be admitted and monitored. These children need aggressive hydration. The use of beta-adrenergic agonists like epinephrine or albuterol, or even steroids, has not been shown to be effective in children with bronchiolitis. Instead, these children should be provided with humidified oxygen and nebulized hypertonic saline. Ensuring that the infant is well hydrated is key, especially for those who cannot eat. Oxygen therapy to maintain saturations just above 90% is adequate.

Children who develop signs of severe respiratory distress may progress to respiratory failure. These children may require intensive care for mechanical ventilation or non-invasive support. A high-flow nasal cannula is an emerging modality of non-invasive support for children with bronchiolitis. Clinical trials are in progress.

Passive immunization against RSV is available with palivizumab for those who are at the greatest risk for severe illness. During the RSV season, this requires monthly injections of the drug, but this may not only be expensive but not also not practical for most infants.

Current recommendations by the American Academy of Pediatrics support the use of palivizumab during the first year of life for children with a gestational age less than 29 weeks, symptomatic congenital heart disease, chronic lung disease of prematurity, neuromuscular disorders that make it difficult to clear the airways, airway abnormalities, and immunodeficiency. Prophylaxis may be continued in the second year of life for children who require continued interventions for chronic lung disease of prematurity or those who remain immunosuppressed.

## 2. Methodology

**Study Design**
A randomized, prospective, comparative clinical trial was conducted at the Department of Pediatrics at ACS Medical College from November 2022 to January 2024, including children aged 3 to 24 months admitted with the diagnosis of bronchiolitis.

**Definitions**
1) Bronchiolitis was defined as first episode of expiratory wheeze of acute onset in a child less than 2 years of age who has signs of viral respiratory illness like coryza, otitis media or fever with or without indications of respiratory distress, with chest x-ray showing marked generalized emphysema, patchy consolidation, atelectasis and abnormal linear shadows, due to thickening of the bronchioles.[1]
2) Tachypnoea: based on WHO ARI criteria child was considered tachypnoeic if the respiratory rate was
   a) 60/min or more for age < 2 months
   b) 50/min or more for age 2-12 months
   c) 40/min or more for age > 12 months
3) Respiratory distress was defined as the presence of subcostal, intercostal, supersternal or supraclavicular recessions.

**Inclusion Criteria**

Children aged 3 months to 24 months with clinical presentation of acute bronchiolitis which is defined as first episode of wheezing along with prodrome of upper respiratory tract infection including rhinorrhea, cough, and sometimes low grade fever which may progress to dysnpnoea.

**Exclusion Criteria:**
Children with-
1) Cardiac disease
2) Previous wheezing episode
3) Chronic respiratory disease
4) Severe disease: saturation < 85% on room air, cyanosis, head bobbing, obtunded consciousness, and/or progressive respiratory distress requiring respiratory support other than supplemental oxygen.
5) Those having received nebulized hypertonic saline within the previous 12 hours - also excluded.

Children admitted with the diagnosis of acute bronchiolitis to the paediatric wards who satisfied the inclusion criteria were recruited for the study. 100 children were enrolled for the study based on the sample size required. Written informed consent was obtained from all the parents before enrolling them into the study. Ethical committee approval was obtained from the institution for the study. Patients were randomized into 2 groups using a computer generated random numbers.

Group 1 - Patients will receive 0.1 mg/kg/dose of nebulized Salbutamol followed by 4ml of 3% hypertonic saline solution via nebulizer.
Group 2 - Patients will receive 0.1 mg/kg/dose of nebulized Salbutamol followed by 4ml of 0.9% saline solution via nebulizer.

Patients in each group will receive the intervention at intervals of 4 hours, six times daily until the patient is recovered. Additional inhalations as needed are recorded and calculated as add-on therapy.

Patients are examined at the enrollment and during initial inhalation session and everyday in the morning. The following parameters are measured and recorded using a clinical severity score described by wang et al. Patients who show signs of deterioration will be excluded from the study.

**Admission Criteria**
1) Persistent oxygen saturation level of less than 92%.
2) Increased work of breathing.
3) Inadequate oral intake.

Children who have improved will be discharged.

**Discharge Criteria**-
1) Improvement in oxygen saturation above 92% in room air.
2) Decreased work of breathing with no intercostal retraction.
3) Adequate oral intake.

The duration of hospital stay, was measured using a method previously validated by the Paediatric Investigators Collaborative Network on Infections in Canada studies of hospitalized children with RSV infection [ PICNIC study ] . Each day the child was assessed for the following four reasons which accounted for ongoing hospitalization.
1) Patient receiving drug treatment for bronchiolitis
2) Patient receiving oxygen supplementation or parenteral fluids because of bronchiolitis.
3) Patient hospitalized because of underlying (pre-existing) illness only.

Or

Awaiting transport home or uncertain home environment.
Only those days for which the reason for hospitalization was (1) i.e receiving drug treatment for bronchiolitis or (2) i.e oxygen supplementation or parenteral fluids for bronchiolitis were recorded as valid hospital days for calculation of duration of stay in hospital. Discharge timing was at the discretion of the attending physician.

**Statistical methods**
Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis). Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

## 3. Results

During the study period, a total of 142 patients were admitted with a clinical diagnosis of bronchiolitis. One hundred and twelve of them were eligible for the study and 30 children were excluded in view of previous wheezing episodes. Among the 112 children, 5 were excluded in view of prior treatment with steroids from the referring hospital, 2 patients were excluded because the parents did not consent for treatment, 4 patients developed severe disease on the day of admission and 1 had cardiac disease . Finally 100 patients were included for the analysis, randomized into two groups, 50 patients in Group 1 (3% Saline) and 50 patients in Group 2 (Normal saline).

**Table 4:** Age distribution of subjects in both the groups

| | | Group | | | |
|---|---|---|---|---|---|
| | | 3% Saline | | Normal Saline | |
| | | Count | % | Count | % |
| Age (months) | 0 to 6 Months | 13 | 26.00% | 25 | 50.00% |
| | 6 to 12 months | 19 | 38.00% | 8 | 16.00% |
| | >12 months | 18 | 36.00% | 17 | 34.00% |
| | Mean ± SD | 10.7 ± 6.1 | | 9 ± 6 | |

In Group 1 mean age of subjects was 10.7 ± 6.1 months and in Group 2 was 9 ± 6 months. In Group 1 majority of subjects were in the age group 6 to 12 months (38%) and in Group 2 majority of subjects were in the age group 0 to 6 months. There was no significant difference in mean age and age distribution between two groups.

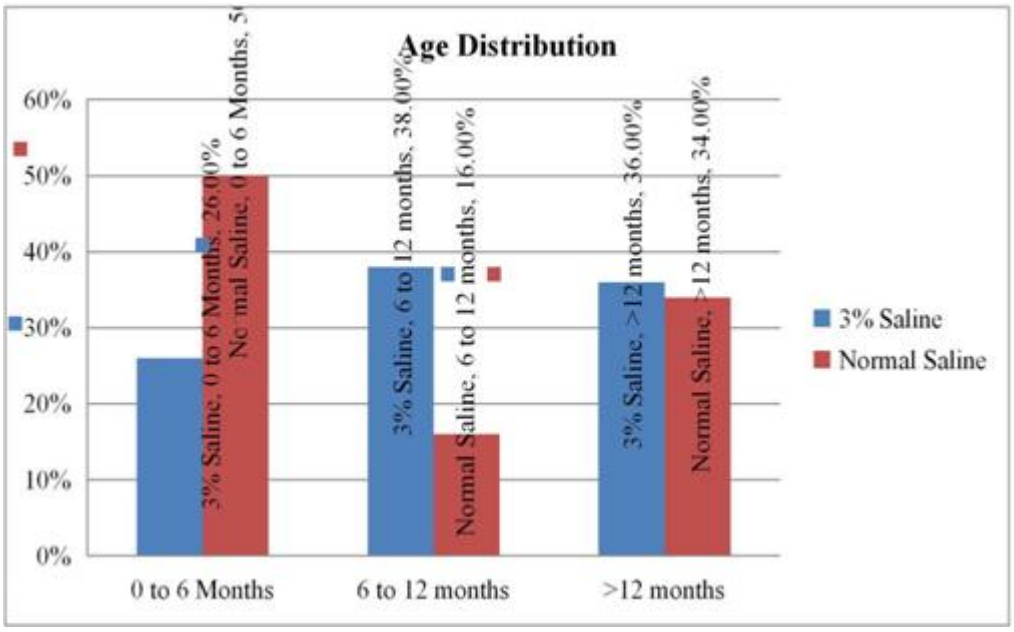


**Figure 6:** Bar diagram showing Age distribution of subjects in both the groups

**Table 5:** Gender distribution of subjects between two groups

| | | Group | | | |
|---|---|---|---|---|---|
| | | 3% Saline | | Normal Saline | |
| | | Count | % | Count | % |
| Gender | Female | 21 | 42.00% | 26 | 52.00% |
| | Male | 29 | 58.00% | 24 | 48.00% |

$\chi 2 = 1.004$, df = 12, p = 0.316

In Group 1, 58% were males and 42% were females and in Group 2, 52% were females and 48% were males. There was no significant difference in gender distribution between two groups.

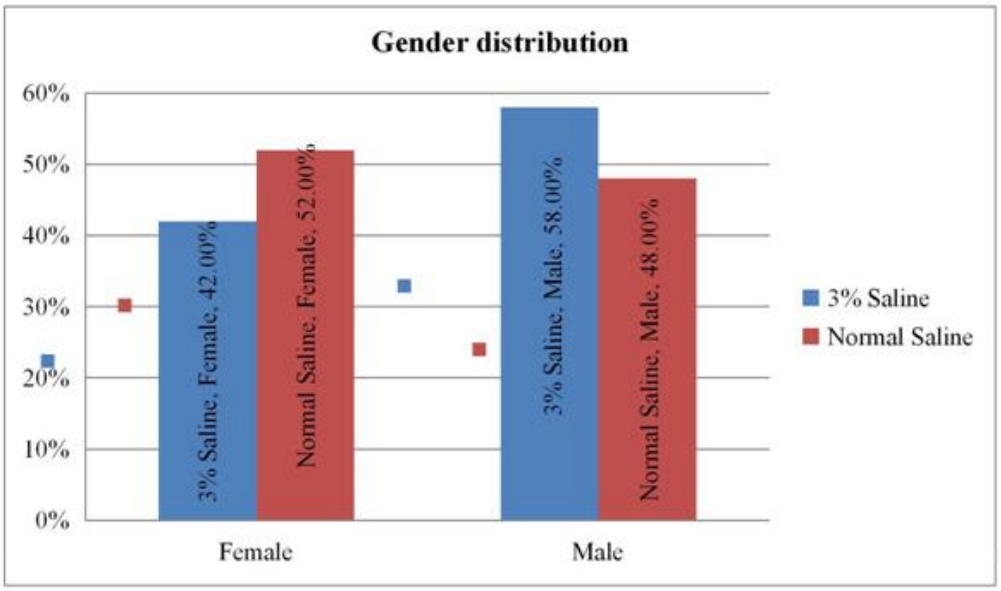


**Figure 7:** Bar diagram showing Gender distribution of subjects between two groups

**Table 6:** Clinical profile of subjects in both the groups

| | | Group | | | | P value |
|---|---|---|---|---|---|---|
| | | 3% Saline | | Normal Saline | | |
| | | Count | % | Count | % | |
| Running Nose | Present | 50 | 100.00% | 50 | 100.00% | - |
| Cough | Present | 50 | 100.00% | 50 | 100.00% | - |
| Hurried breathing | Present | 50 | 100.00% | 50 | 100.00% | - |
| ROF | Absent | 50 | 100.00% | 50 | 100.00% | - |
| Fever | Absent | 5 | 10.00% | 9 | 18.00% | 0.249 |
| | Present | 45 | 90.00% | 41 | 82.00% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Retraction | IC | 26 | 52.00% | 22 | 44.00% | 0.423 |
| | TS | 24 | 48.00% | 28 | 56.00% | |
| Wheeze | Expiratory | 8 | 16.00% | 9 | 18.00% | 0.79 |
| | Expiratory and Inspiratory | 42 | 84.00% | 41 | 82.00% | |

In Group 1, 100% had Running Nose, Cough, Hurried breathing, 0% had ROF, 90% had fever, 52% had IC retraction, 48% had TS retraction, 84% had Expiratory and Inspiratory wheeze and 16% had Expiratory wheeze.

In Group 2, 100% had Running Nose, Cough, Hurried breathing, 0% had ROF, 82% had fever, 44% had IC retraction, 56% had TS retraction, 82% had Expiratory and Inspiratory wheeze and 18% had Expiratory wheeze.

There was no significant difference in clinical profile between two groups.

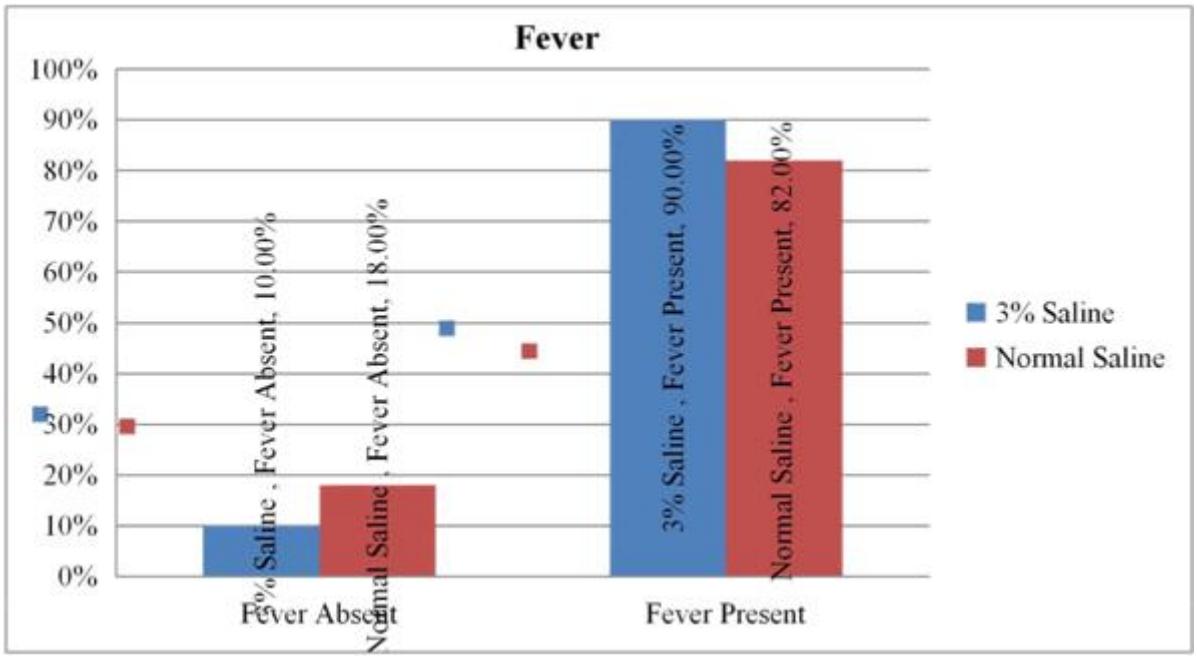


**Figure 8:** Bar diagram showing Fever comparison between two groups

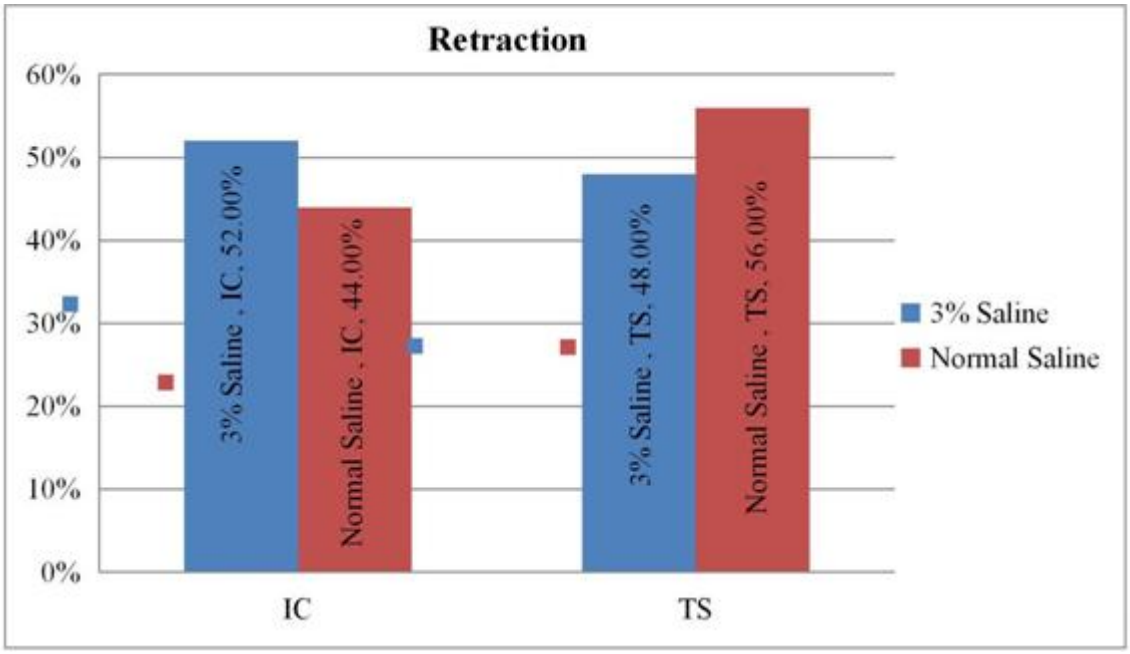


**Figure 9:** Bar diagram showing Retraction comparison between two groups

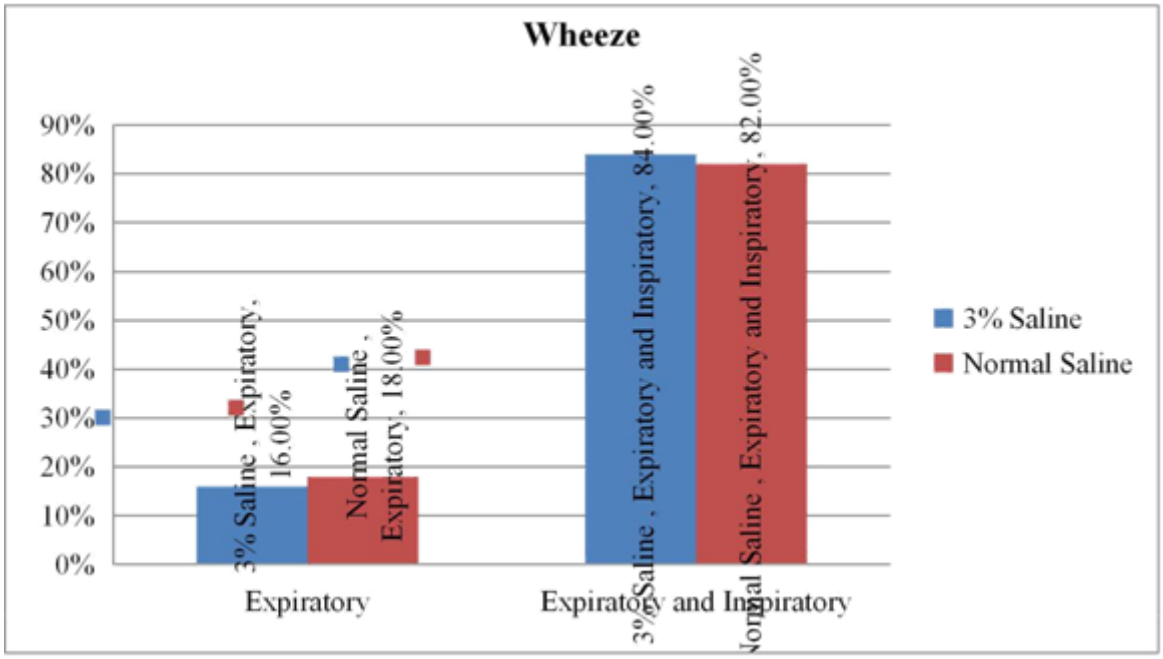


**Figure 10:** Bar diagram showing Wheeze comparison between two groups

**Table 7:** Respiratory rate comparison between two groups

| | | RR | | | | | P value |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Median | Minimum | Maximum | |
| Group | 3% Saline | 55.6 | 4.6 | 55 | 44 | 66 | 0.587 |
| | Normal Saline | 55 | 5.6 | 54 | 42 | 66 | |

Mean RR in Group 1 was 55.6 ± 4.5 cpm and in Group 2 was 55 ± 5.6 cpm. There was no significant difference in RR between two groups.

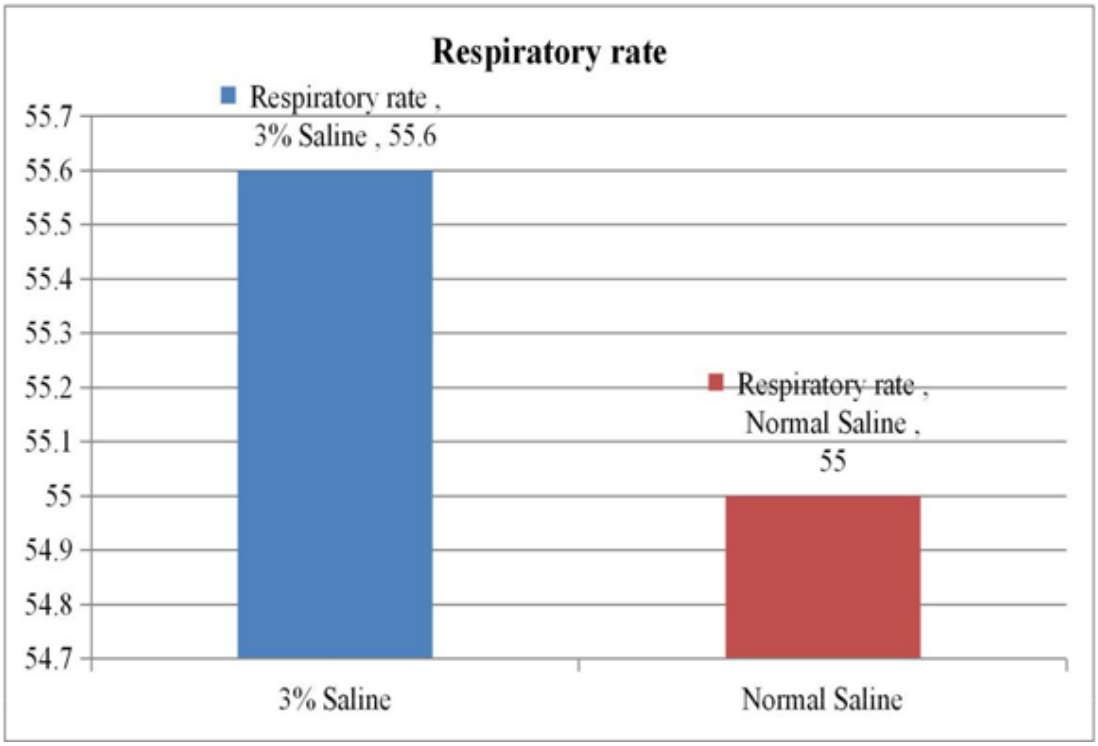


**Figure 11:** Bar diagram showing Respiratory rate comparison between two groups

**Table 8:** SAO2 comparison between two groups

| | | SAO2 | | | | | P value |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Median | Minimum | Maximum | |
| Group | 3% Saline | 94.6 | 1.2 | 95 | 92 | 98 | 0.379 |
| | Normal Saline | 94.4 | 1.3 | 95 | 90 | 96 | |

Mean SAO2 in Group 1 was 94.6 ± 1.2 and in Group 2 was 94.4 ± 1.3. There was no significant difference in mean SAO2 between two groups.

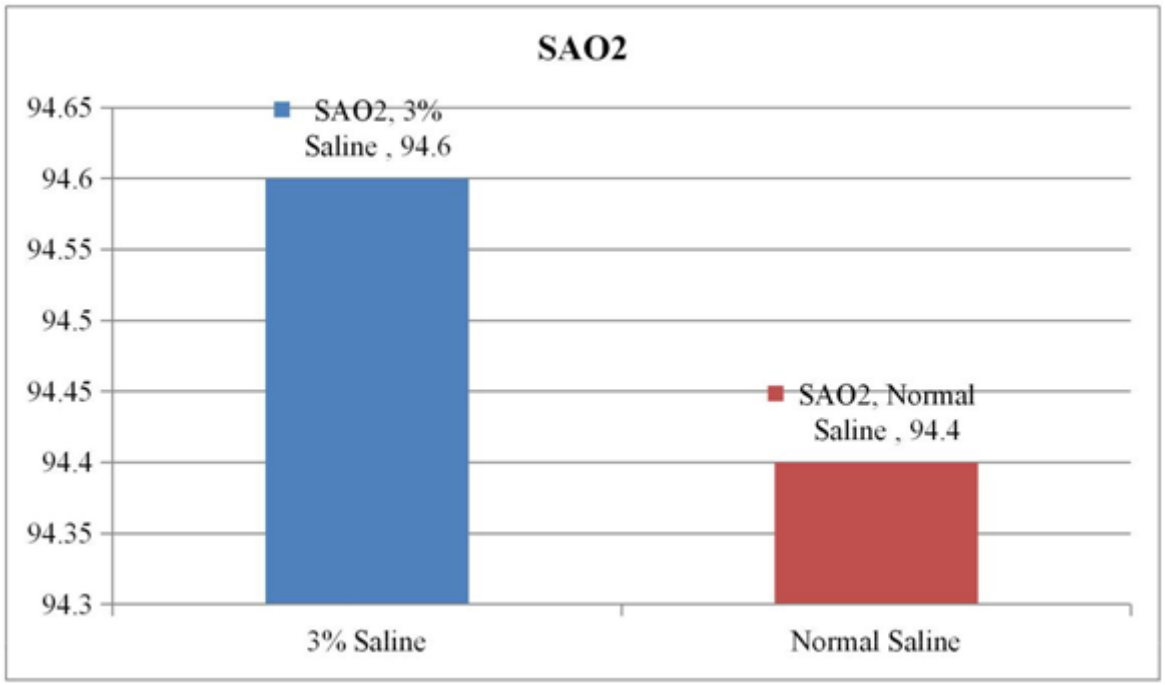


**Figure 12:** Bar diagram showing SAO2 comparison between two groups

**Table 9:** SAO2 comparison between two groups

| | | Group | | | |
|---|---|---|---|---|---|
| | | 3% Saline | | Normal Saline | |
| | | Count | % | Count | % |
| General Condition | Normal | 50 | 100.0% | 50 | 100.0% |
| Family History of Asthma | Absent | 50 | 100.0% | 50 | 100.0% |
| O2 | R | 50 | 100.0% | 50 | 100.0% |

In both the groups 100% had normal general condition, none had family history and O2

**Table 10:** Clinical Score Comparison between two groups at different intervals of followup

| | | Group | | | | | | | P value |
|---|---|---|---|---|---|---|---|---|---|
| | | 3% Saline | | | Normal Saline | | | | |
| | Count | Mean | SD | Median | Count | Mean | SD | Median | |
| 0 HRS | 50 | 5.4 | 0.7 | 5 | 50 | 5.5 | 0.7 | 6 | 0.296 |
| D 1 | 50 | 4.6 | 0.9 | 5 | 50 | 4.9 | 0.9 | 5 | 0.086 |
| D2 | 50 | 3.7 | 0.9 | 4 | 50 | 4.1 | 0.9 | 4 | 0.011* |
| D3 | 34 | 2.8 | 0.8 | 3 | 38 | 3.6 | 1.2 | 3 | 0.005* |
| D4 | 21 | 1.4 | 0.6 | 1 | 29 | 2.9 | 1.6 | 2 | <0.001* |
| D5 | 3 | 1.3 | 0.6 | 1 | 16 | 3.6 | 2 | 5 | 0.08 |
| D6 | 0 | . | . | . | 10 | 4.4 | 1 | 5 | - |

*Mann Whitney U test

In Group 1, median Clinical score at 0 hrs was 5, at Day 1 was 5, at day 2 was 4, at day 3 was 3, at day 4 and day 5 was 1 respectively. In Group 2, median Clinical score at 0 hrs was 6, at Day 1 was 5, at day 2 was 4, at day 3 was 3, at day 4 was 2, at day 5 was 5 and at day 6 was 5 respectively.

Significant difference in Median Clinical score was observed between two groups at Day 2, Day 3 and Day 4. On these days clinical score was high in Normal saline group than in 3% saline group.

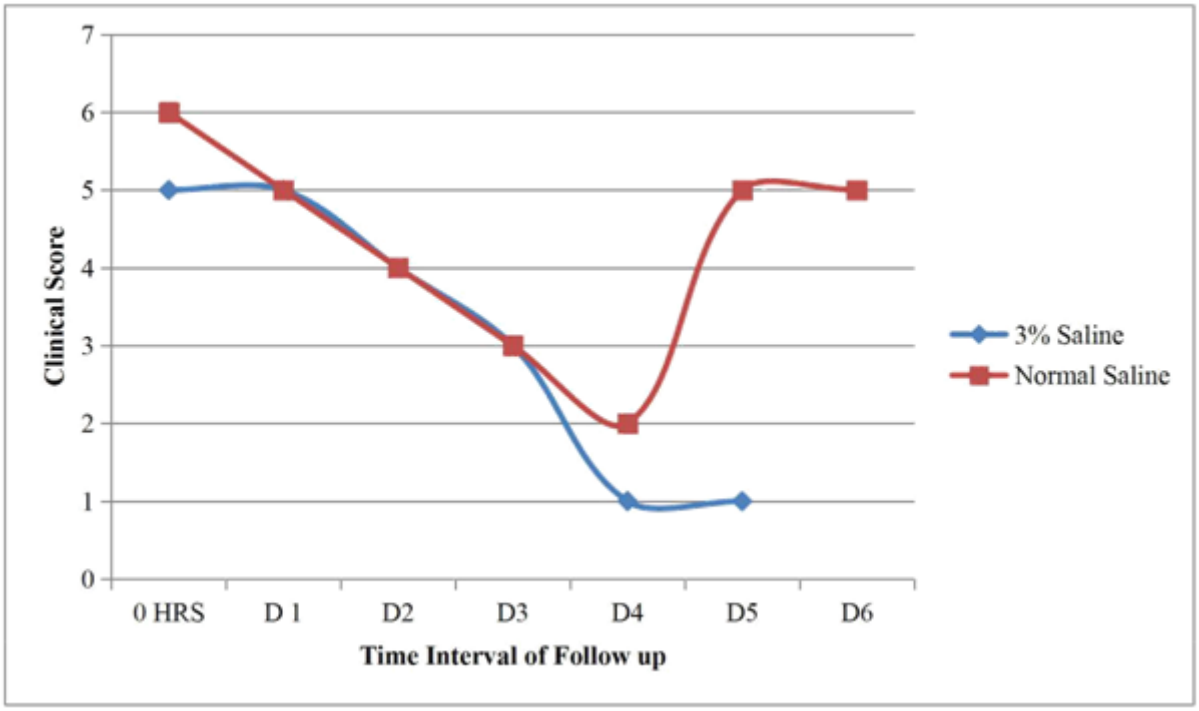


**Figure 13:** Line diagram showing Clinical Score Comparison between two groups at different intervals of followup

**Table 11:** Reduction in clinical severity comparison between two groups

| | Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3% Saline | | | Normal Saline | | | |
| | Mean | SD | Median | Mean | SD | Median | P value |
| Reduction in clinical severity | 1.5 | 0.5 | 1 | 1.4 | 0.5 | 1 | 0.392 |

In Group 1, mean Reduction in clinical severity was 1.5 ± 0.5 and in Normal saline group mean Reduction in clinical severity was 1.4 ± 0.5. There was no significant difference in mean reduction in clinical severity between two groups.

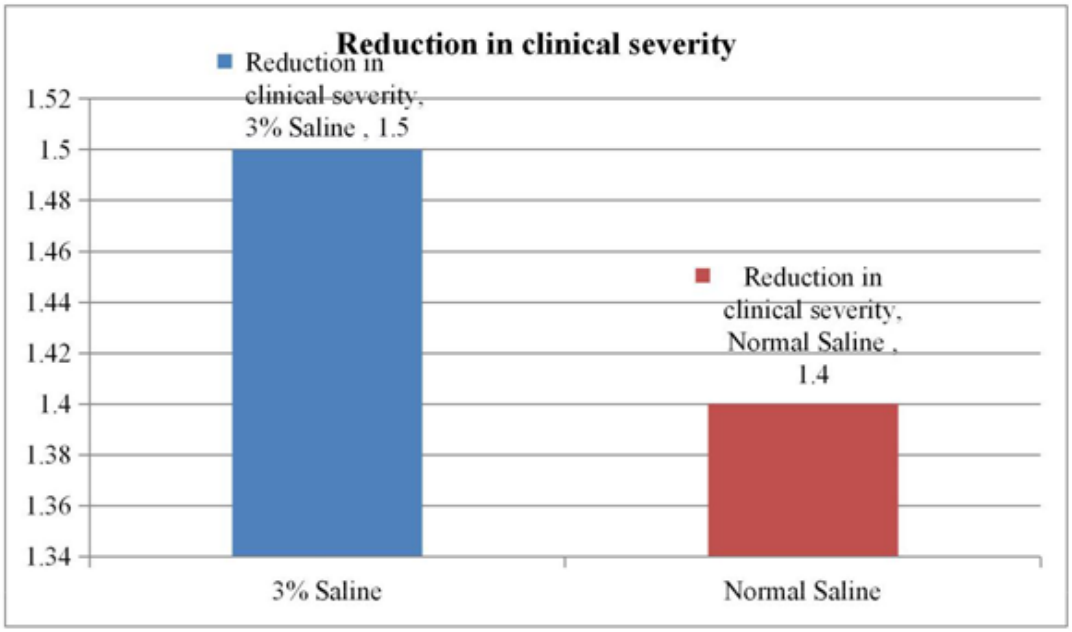


**Figure 14:** Bar diagram showing Reduction in clinical severity comparison between two groups

**Table 12:** Length of stay comparison between two groups

| | Group | | | | | | P value | Mean difference | Percentage reduction in 3% saline group |
|---|---|---|---|---|---|---|---|---|---|
| | 3% Saline | | | Normal Saline | | | | | |
| | Mean | SD | Median | Mean | SD | Median | | | |
| Length of stay –in days | 1.6 | 0.5 | 1.5 | 2.7 | 1.7 | 2 | <0.001* | 1.1 ± 1.2 | 40.70% |

In Group 1, mean Length of stay was 1.6 ± 0.5 days and in Normal saline group mean Length of stay was 2.7 ± 1.7 days. There was significant difference in mean Length of stay between two groups.

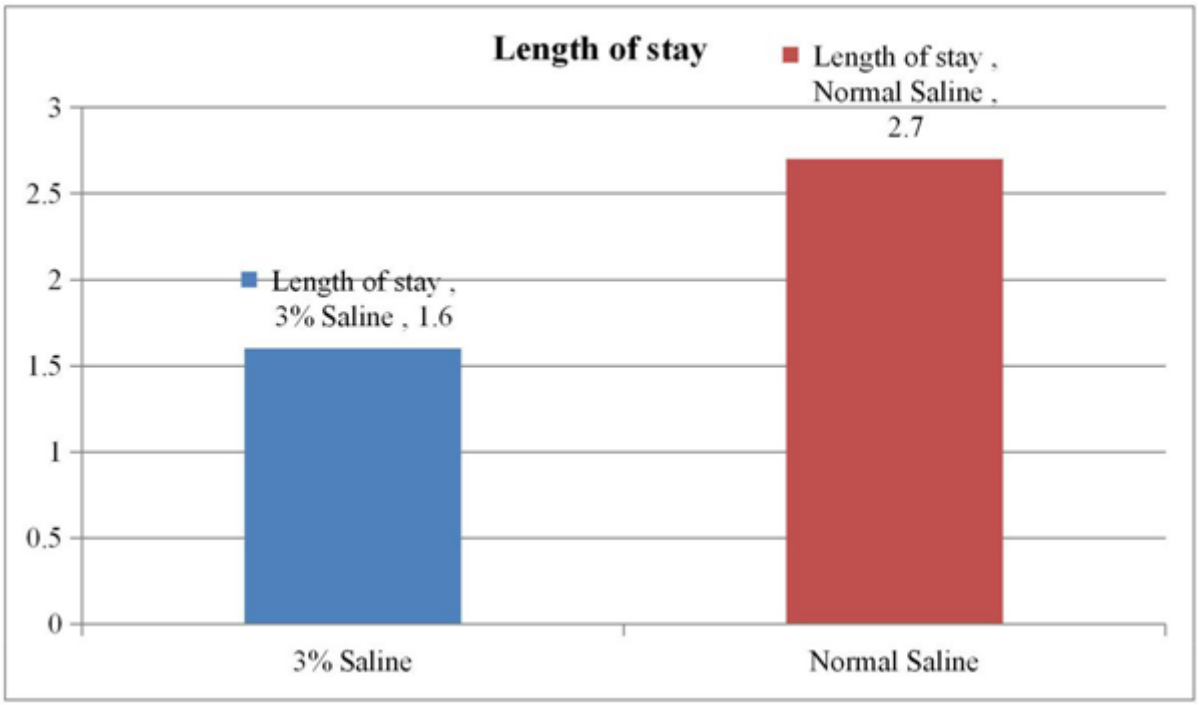


**Figure 15:** Bar diagram showing Length of stay comparison between two groups

**Table 13:** Length of stay distribution between two groups

| | | Group | | | |
|---|---|---|---|---|---|
| | | 3% Saline | | Normal Saline | |
| | | Count | % | Count | % |
| Length of Stay | 1 to 2 days | 44 | 91.70% | 31 | 62.00% |
| | 3 to 4 days | 4 | 8.30% | 10 | 20.00% |
| | >4 days | 0 | 0.00% | 9 | 18.00% |

$\chi$ 2 = 13.79, df = 2, p = 0.001*

In Group 1, 91.7% stayed for 1 to 2 days, 8.3% stayed for 3 to 4 days and in Group 2, 62% stayed for 1 to 2 days, 20% stayed for 3 to 4 days and 18% stayed for >4 days. Subjects in Group 2 stayed for longer duration than in Group 1. There was significant difference in Length of stay between two groups.

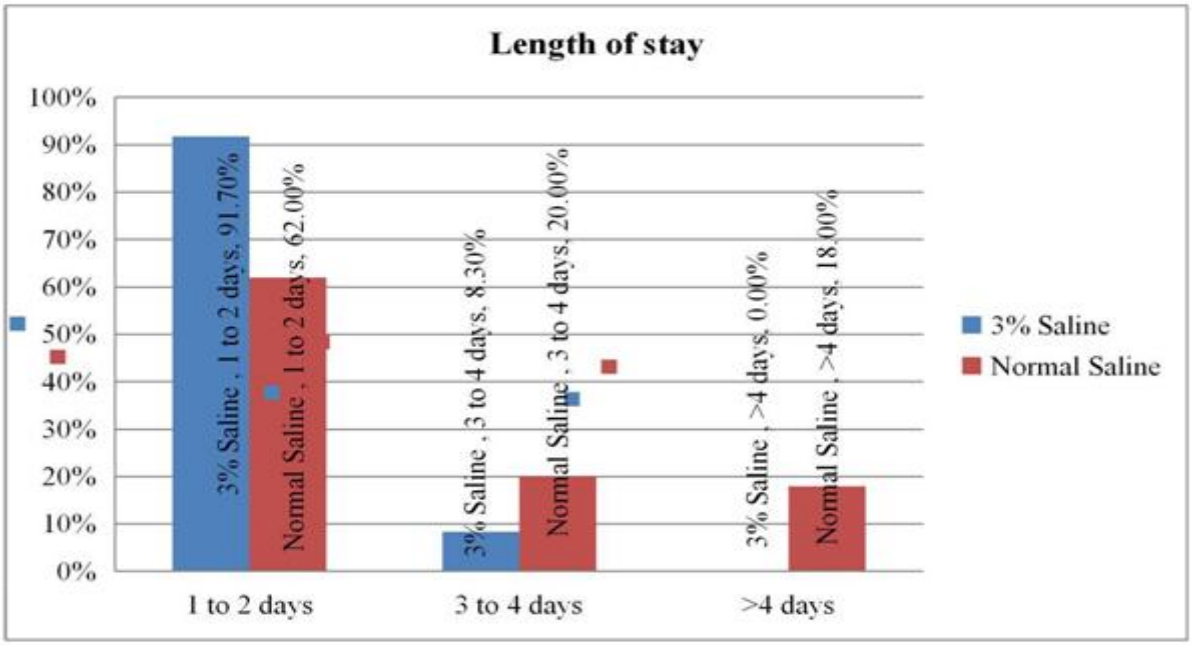


**Figure 16:** Bar diagram showing Length of stay distribution between two groups

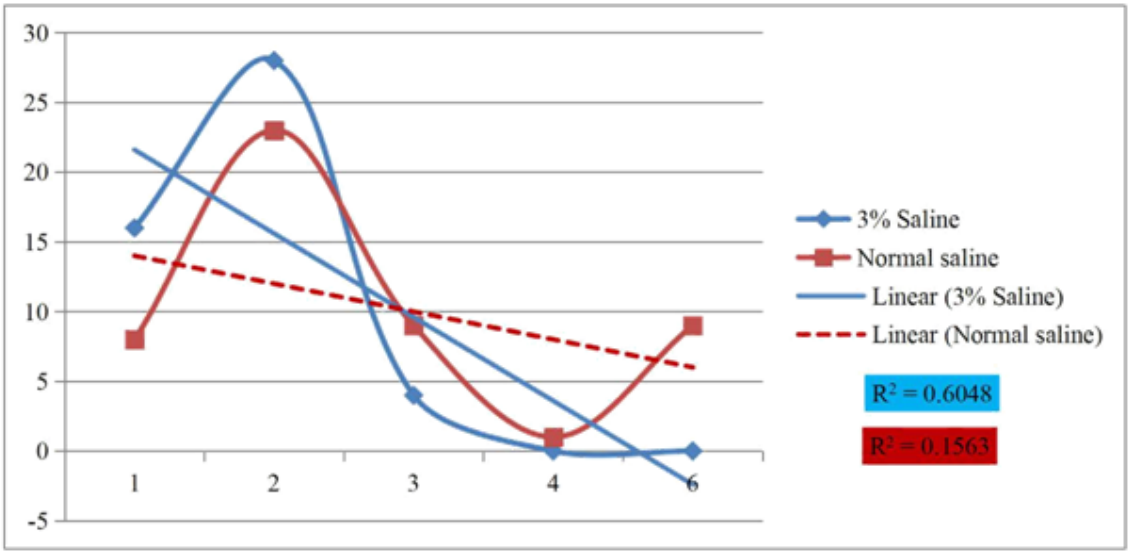


**Figure 17:** Number of Patients in each group remaining in Hospital

A linear regression analysis was done to find out if there would have been any difference if more number of patients were enrolled. Although there was a trend, favouring towards use of 3% saline. The difference was statistically significant.

**Table 14:** Add-on therapy distribution between two groups

| | | Group | | | |
|---|---|---|---|---|---|
| | | 3% Saline | | Normal Saline | |
| | | Count | % | Count | % |
| Add-on therapy given | No add on therapy | 17 | 34.0% | 10 | 20.0% |
| | Add on Therapy given | 33 | 66.0% | 40 | 80.0% |

$\chi 2 = 2.486$, df = 1, p = 0.115

In Group 1, 66% were given add on therapy and in Group 2, 80% were given add on therapy. However there was no statistically significant difference in add on therapy given between two groups.

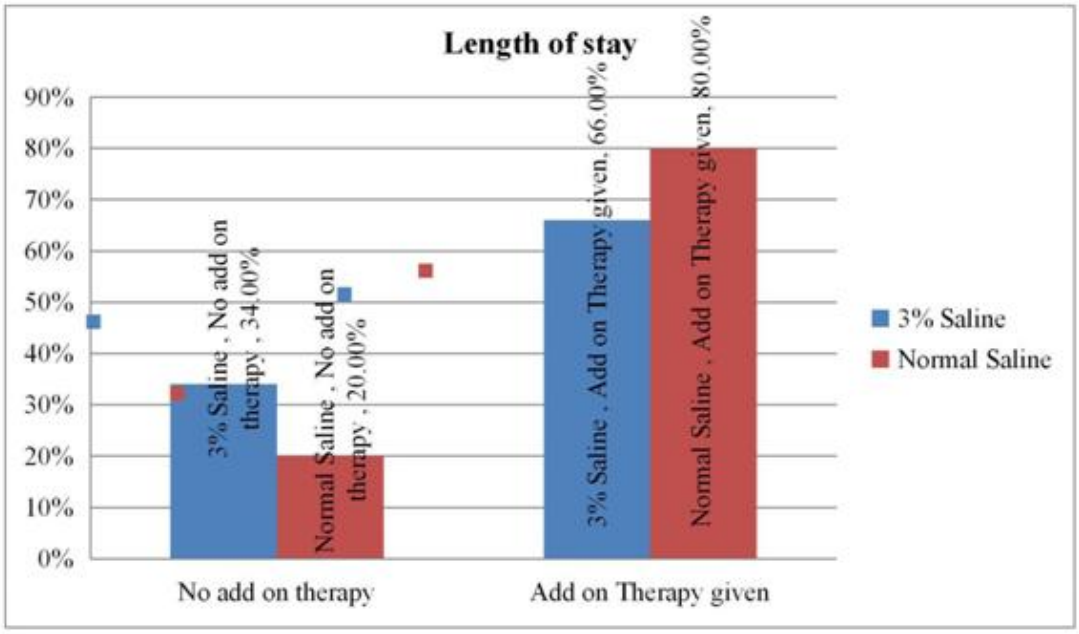


**Figure 18:** Bar diagram showing length of stay with and without add on therapy distribution between two groups

**Table 15:** Number of add-on therapy distribution between two groups

| | Group | | | | | | P value |
|---|---|---|---|---|---|---|---|
| | 3% Saline (n = 33) | | | Normal Saline (n = 40) | | | |
| | Mean | SD | Median | Mean | SD | Median | |
| Number of add-on therapy given | 2.8 | 1 | 2 | 3 | 1.6 | 2 | 0.452 |

In Group 1, out of 33 subjects who were given add on therapy, mean add on therapy given was 2.8 ± 1 and in Group 2, out of 40 subjects who were given add on therapy, mean add on therapy given was 3 ± 1.6. There was no significant difference in number of add on therapy given between two groups.

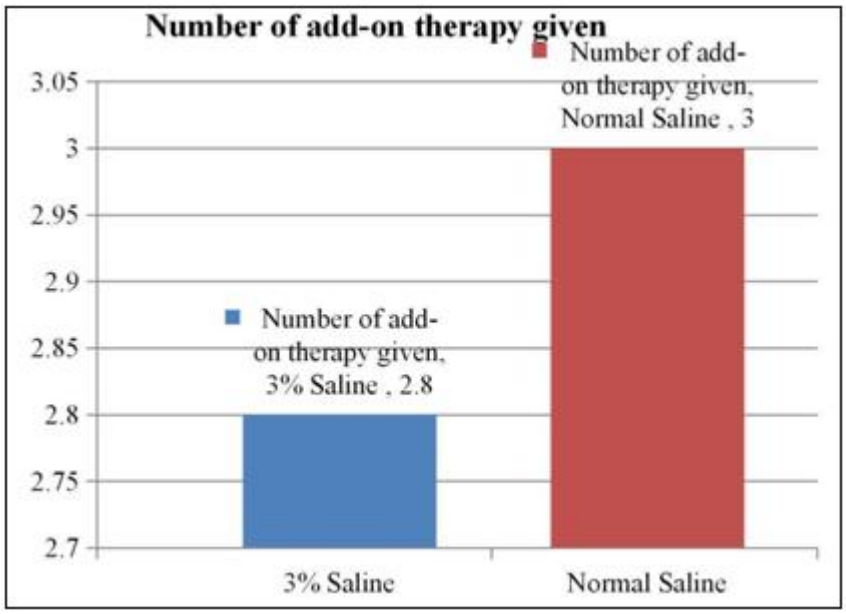


**Figure 19:** Bar diagram showing Number of add-on therapy distribution between two groups

**Table 16:** Outcome comparison between two groups

| | | Group | | | |
|---|---|---|---|---|---|
| | | 3% Saline | | Normal Saline | |
| | | Count | % | Count | % |
| Outcome | Discharged | 50 | 100.00% | 41 | 82.00% |
| | Failure | 0 | 0.00% | 9 | 18.00% |

$\chi 2 = 9.89$, df = 1, p = 0.002*

In Group 1, 100% of subjects were discharged and in Group 2, 82% were discharged and 18% had failure. This difference in outcome between two groups was statistically significant.

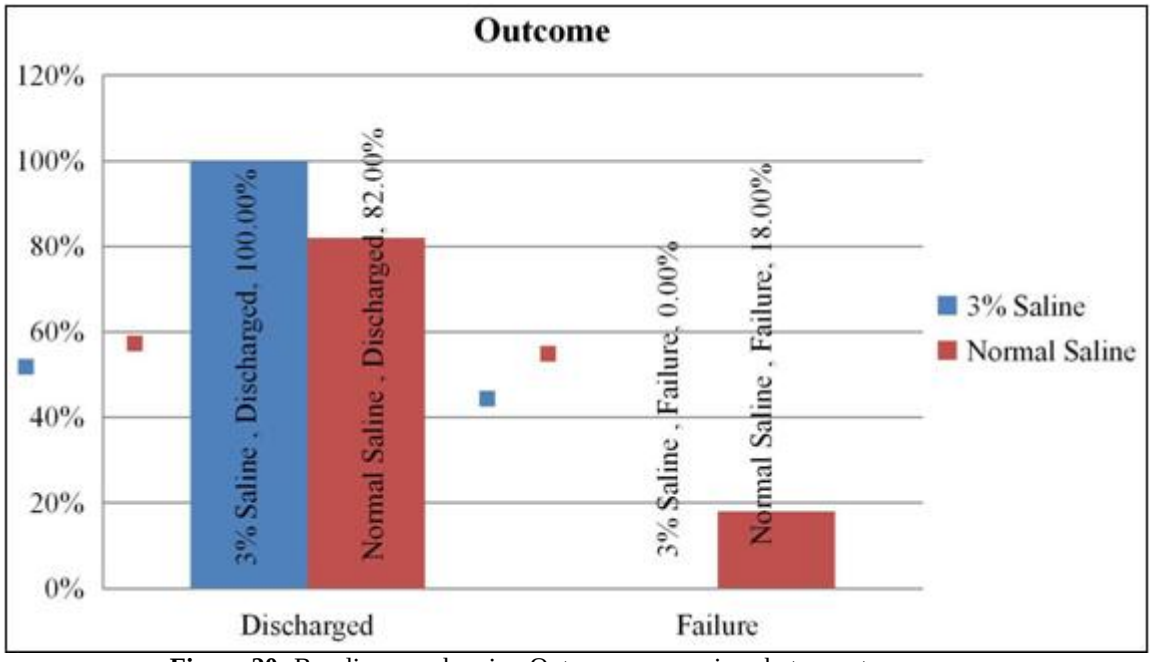


**Figure 20:** Bar diagram showing Outcome comparison between two groups

The principle outcome parameters studied in the study were in the length of the hospital stay. The mean reduction in clinical severity with 3 % hypertonic saline was 1.5 ± 0.5 which was slightly better than normal saline (1.4 ± 0.5). There was no significant difference between two groups. The mean duration of hospital stay with hypertonic saline was 1.6 ± 0.5 days which was shorter than with normal saline 2.7 ± 1.7 days. There was significant difference in

length of stay in hospital between two groups. Sixty six percent of the patients receiving hypertonic saline were given add on therapy and 80% of the patients receiving normal saline were given add on therapy. However there was no statistically significant difference in add on therapy given between two groups. When we took the overall outcome into account, 18% of patients receiving normal saline nebulisation had treatment failure and none of the patients receiving hypertonic saline had treatment failure. This difference was statistically significant with p-value of 0.002.

## 4. Conclusion

In conclusion, findings of our study do not suggest that 3% saline is superior to normal saline in terms of reducing clinical severity and number of additional nebulizations in hospitalized children with moderate severity of acute bronchiolitis.

However 3% saline nebulization was found to be safe and prevented worsening of symptoms in children with acute bronchiolitis.

Further studies are required to find out whether 3% saline prevents/or reduces the worsening of symptoms, as observed in our study.

In our study, length of stay in hospital was found to be less in patients who recived 3% hypertonic saline as compared to patients who received normal saline.

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