RESEARCH ARTICLE

Efficacy of newer modalities in the management of indirect hyperbilirubinaemia at a secondary care hospital: A prospective study from 2015-2018

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Abstract

Objective: To evaluate the efficacy of current practices and new modalities for the management of neonatal indirect hyperbilirubinaemia.

Methods: The prospective study was conducted at King Khalid Hospital, Al Majmaah, Saudi Arabia, from September 2015 to September 2018, and copmprised neonates with hyperbilirubinaemia who were managed using the National Institute for Health and Clinical Excellence 2010 guidelines. The outcomes were measured in terms of decrease in total serum bilirubin and clinical improvement. Data was analysed using SPSS 25.

Results: Of the 233 subjects, there were 119(51%) girls and 114(49%) boys. Phototherapy was used in 162(69.5%) cases, intensive phototherapy in 36(15.5%) and intravenous immunoglobulin in 35(15%). Exchange transfusion was done in 2(0.85%) patients. All the 233(100%) patients improved with the management and total serum bilirubin significantly reduced ($p<0.05$).

Conclusion: Newer techniques were found to have a vital role in the management of neonatal hyperbilirubinaemia.

Keywords: Neonatal jaundice, Intensive phototherapy, Exchange transfusion. (JPMA 70: 1753; 2020)

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Introduction

Neonatal jaundice (NNJ) is a common condition affecting 60% of the healthy newborns.[1,2] Total serum bilirubin (TSB) rises because of imbalance between bilirubin production and ability to conjugate and clear the bilirubin load which occurs as a result of increased red cell metabolism.[3-5] Most of the cases are caused by physiological jaundice and is usually harmless. Certain risk factors are associated with severe neonatal hyperbilirubinaemia. These include prematurity, low birth weight (LBW), jaundice in the first 24 hours of life, mother with blood group O or rhesus (RH) negative, Glucose-6-Phosphate dehydrogenase (G6PD) deficiency, rapid rise of TSB, high pre-discharge bilirubin level, cephalohematomas or bruises, babies of diabetic mothers and family history of severe NNJ in siblings.[6,7]

High serum bilirubin >425-510µmol/L (25-30 mg/dL) can cross the blood-brain barrier and lead to acute or chronic bilirubin toxicity.[4,8] Acute bilirubin toxicity can progress from poor feeding, lethargy, high-pitch cry, hypo- or hyper-tonia, ultimately leading to fever, apnoea, seizures and death. Chronic toxicity or kernicterus is characterised by dyskinetic cerebral palsy (CP), hearing deficits and sometimes intellectual deficits.[9-12]

Guidelines have been formulated by the American Academy of Paediatrics (AAP) and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom for the management of neonatal jaundice.[13]

Guidelines should be followed for the management of these cases as hyperbilirubinaemia can lead to toxicity.[6] Rapid bilirubin reduction can be achieved by using intensive phototherapy (IP), exchange transfusion (ET) and drugs.[4,14]

IP is the choice of management for lowering bilirubin in 2-4 hours,[15,16] while ET can reduce bilirubin in 1-2 hours.[17-21] Phototherapy and ET are the mainstay of treatment for NNJ.[22,23] Blue light (380-550nm) is the most effective treatment. However, certain side effects, like skin rashes, vomiting, diarrhoea and temperature irregularities, may be seen.[24-27]

ET, an invasive procedure, is occasionally indicated for NNJ, especially in the presence of bilirubin encephalopathy. The procedure may be associated with serious complications like apnoea, necrotising enterocolitis, and sepsis in up to 5% cases.[28-31]

Intravenous immunoglobulins (IVIGs) can be used in patients with incompatibility between blood groups A, B, O, AB (ABO) and Rh.[14]

The current study was conducted to evaluate the efficacy of current practices and new modalities, like IP, for the management of neonatal indirect hyperbilirubinaemia.

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Patients and Methods

The prospective study was conducted at King Khalid Hospital, Al-Majmaah, Saudi Arabia, from September 2015 to September 2018. All the consecutive cases presenting during this time period was the sample size i.e., 233. Complete enumeration sampling method based on the inclusion criteria was used to collect the data. The sample comprised neonates with jaundice diagnosed by visual, transcutaneous or serum bilirubin assessment. Neonates with direct hyperbilirubinaemia were excluded.

After approval from the institutional ethics review committee, the NICE 2010 guidelines for the management of jaundiced neonates were used.[13] Informed consent was obtained from the parents before collecting the data.

Blood groups of mothers and neonates were noted. Transcutaneous bilirubin (TCB) and TSB were checked for all patients at baseline (TSB1). Repeat TSB was checked after the first four hours (TSB2). Further TSB assessments were done every 4-6 hours, and final reading was taken at the end of treatment for all patients (TSB3).

Indirect fraction was checked for all patients and those with higher TSB reaching the threshold of treatment or certain risk factors like ABO or Rh incompatibility or history of severe NNJ in a sibling were further investigated with complete blood count (CBS), including haemoglobin (Hb) and haematocrit (Ht), peripheral blood smear, reticulocyte counts, and direct antiglobulin test.

Phototherapy was started with conventional units for all patients falling in the phototherapy zone. Patients with higher bilirubin level or falling in the lower part of the ET zone, according to NICE graphs for NNJ, were immediately given IP (Bilisphere 360 LED).

Patients with signs of bilirubin toxicity or with bilirubin levels high in the zone underwent ET. Standard care and precautions were taken for all the cases during the therapy. Clinical condition and bilirubin were closely monitored for all cases.

IVIGs were given in cases of ABO and Rh incompatibility with severe jaundice requiring IP or ET. Patients were monitored for the adverse effects of treatment modalities. Outcomes were measured based on bilirubin reduction and clinical improvement. Data was analysed using SPSS 25. Normality of quantitative data was checked by one-sample Kolmogorov-Smirnov test. Frequencies and percentages were reported for qualitative variables. Median (25th-75th percentile) was calculated for non-normally distributed quantitative variables. Friedman test with Bonferroni correction was used to analyse the before and after differences in TSB levels. To carry out post-hoc analysis, Wilcoxon signed-rank test was used. $P<0.05$ was considered statistically significant.

Results

Of the 233 subjects, there were 119(51%) girls and 114(49%) boys. Overall, 124(53%) neonates were delivered by Caesarean section (CS). The most common maternal blood group was O +ve in 107(46%) cases, while

Table-1: Treatment options used for neonatal jaundice.

Diagnosis	Phototherapy	Intensive phototherapy	IV immunoglobulin	Exchange transfusion
Physiological Jaundice	91	1	0	0
ABO incompatibility	65	30	30	1
Rh incompatibility	31	5	5	1
Jaundice of prematurity	26	0	0	0
Blood extravasation	5	0	0	0

ABO: Blood groups O, A, B and AB; Rh: Rhesus.

Table-2: Bilirubin levels before and after the treatment.

TSB1 Median (25th - 75th percentile) n = 197	TSB2 Median (25th - 75th percentile) n = 197	TSB3 Median (25th - 75th percentile) n = 197	p-value
194 (161 - 245) **	240 (189 - 290) **	190 (154 - 213) **	< 0.001*

*Friedman test statistically significant at 5% level of significance

**Wilcoxon Signed Rank Test for multiple comparisons significant at 5% level of significance

TSB: Total serum bilirubin.

Table-3: Bilirubin levels before and after treatment in severe neonatal jaundice.

TSB1 Median (25th - 75th percentile) n = 36	TSB2 Median (25th - 75th percentile) n = 36	TSB3 Median (25th - 75th percentile) n = 36	p-value
256 (211 - 345) **	313 (268 - 383) **	211 (198 - 277) **	< 0.001*

*Friedman test statistically significant at 5% level of significance.
**Wilcoxon Signed Rank Test for multiple comparisons significant at 5% level of significance.
TSB: Total serum bilirubin.

the most common blood group for neonates was A +ve 119(51%). Those with physiological jaundice were 104 (44.6%), followed by ABO incompatibility 67(28.8%), Rh incompatibility 3113.3%), jaundice of prematurity 26 (11.2%) and blood extravasation 5(2.1%) cases. The most common co-morbid condition was respiratory distress syndrome in 39(16.7%) cases.

Reticulocyte counts were raised in 44(19%) cases of ABO incompatibility and 6(2.6%) cases of Rh incompatibility. The direct antiglobulin test was positive in 32(14%) cases of ABO incompatibility and 2(0.8%) cases of Rh incompatibility.

Values of transcutaneous bilirubin assessment and TSB1 were not significantly different (p=0.642)

Phototherapy was used in 218(93.5%) cases, IP in 36(15.5%) and IVIG in 35(15%), while ET was done in 2(0.85%) patients.

IP was administered in 30(12.8%) patients of ABO incompatibility, 5(2.14%) cases of Rh incompatibility, and 1(0.4%) case of physiological jaundice (Table-1).

The most common adverse effect of phototherapy was skin rashes in 27(11.6%) cases, followed by feeding intolerance 26(11.2%) and diarrhoea in 12(5.2%) patients. ET was performed in 2(0.8%) patients each with ABO and Rh incompatibility.

Significant difference was observed in all TSB values (p<0.001). Median TSB1 was significantly less than the median TSB2 (p<0.001), while median TSB1 was significantly higher compared to median TSB3 (p<0.001). TSB3 median value compared to median TSB2 value showed significant reduction in bilirubin (p<0.001) (Table-2).

Among those with severe NNJ, there was a significant difference in all TSB values (p<0.001). Median TSB1 value was significantly less than TSB2 (p<0.001), while median TSB3 value was significantly lower compared to median TSB1 (p<0.001). TSB3 median value, when compared with median TSB2, showed significant reduction in bilirubin (p<0.001) (Table-3).

There was no death or referral to a higher centre. All 233(100%) patients improved with the management and were discharged without any acute or chronic bilirubin toxicity.

Discussion

ABO incompatibility remains a significant cause of severe NNJ followed by Rh incompatibility,[32] which was also observed in the current study where ABO incompatibility was present in 30(83%) cases followed by Rh incompatibility in 5(14%) cases of severe NNJ. However, physiological jaundice was the most common cause of NNJ in the current study. Also, in the current study, 48% cases were preterm babies which is in line with similar studies reporting 37% and 31%.[32,33]

We found that transcutaneous bilirubin assessment was quite reliable and helpful in the early detection and follow-up of jaundiced newborns, which is emphasized by earlier studies as well.[1,34]

Some studies used AAP guidelines for the management of hyperbilirubinaemia.[35,36] However, we followed the NICE guidelines and used phototherapy in 218(93.5%) cases which contrasts with a study reporting 62.6% patients.[32] We used IP in only 36(15.5%) cases, while some other studies used it in all patients of hyperbilirubinaemia.[35] One study compared the effect of conventional and intensive phototherapy and found better outcome with IP.[36] Adverse effects of phototherapy are generally not severe and are well-tolerated[24] which is also consistent with our study where 27% cases had minor adverse effects.

Use of IVIG is well known in NNJ management, and it has been documented by certain studies to result in decreasing the need of ET[37] while we found that combined use of IVIG and IP was an effective means of treatment in severe NNJ.

We used ET in 2(0.85%) cases, while higher rates are found in other studies.[32,36] Certain parts of the world still have higher ET rates.[29] The low ET rate in the current study is most likely due to earlier use of effective phototherapy (conventional and intensive) and IVIG, earlier detection of serum bilirubin levels and follow-up of at-risk cases. This trend has been observed by other studies as well.[38]

The outcome of our patients was quite good as all of them improved with the treatment, and none developed acute or chronic bilirubin toxicity. Studies have documented the incidence of kernicterus, but it was not observed in the current study.[32]

There was no fatal outcome in our study, whereas one study has displayed low mortality rate in neonatal hyperbilirubinaemia treated with ET.[39] Also, some studies have demonstrated high mortality.[32,40] It has been suggested that better techniques should be used for the visual assessment and treatment of NNJ.[8] Further population-based studies should be conducted to ascertain the magnitude of this problem.

Conclusion

The newer techniques, including transcutaneous bilirubin assessment, IVIG and IP were found to have a vital role in the management of NNJ, while ET is still a lifesaving procedure for these patients.

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Conflict of Interest: None.

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