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A Study to See The Efficacy of IGM Enriched IVIG in Reducing Mortality in Neonatal Sepsis

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Abstract

Objective: To study the role of IgM enriched IVIg in reducing mortality in neonatal sepsis. ***Method:*** It is a prospective randomized study conducted in Special Newborn Care Unit(SNCU) of CNMCH, Kolkata over a period of two years (June 2016 – May 2018).Two groups of 248 newborn each (matched for gestational age, sex, weight and other variables) were randomly allocated to receive either antibiotics alone (control group) and antibiotics plus IgM enriched IVIg intravenously (5ml/kg/day) for 4 days(Immunotherapy Group). ***Result:*** Mortality from sepsis in control group was 88/248 (35.5%) of which death from culture proven sepsis was 70/182 (38.5%) and culture negative sepsis was 18/66 (27.3%).In immunotherapy group overall mortality was 40/248(16.1%) of which death from culture proven sepsis was 32/192 (16.7 %) and culture negative sepsis was 8/56(14.2%).***Conclusion:*** We conclude that IgM enriched IVIg therapy in conjuction with antibiotic significantly reduces mortality in neontal sepsis,particularly in culture positive cases.

Key words: Special newborn care unit, immunotherapy group, IgM enrinched IVIg, neonatal sepsis.

AIM: To study the role of IgM enriched IVIg in neonatal sepsis.

Hypothesis: Bacterial infections during the first month of life remains a major cause of mortality and morbidity despite improved perinatal care and development of new generation broad spectrum antimicrobial drugs [1-5].Theoretical arguments of the use of intravenous immunoglobin(IVIg) therapy in neonatal sepsis is very strong[6]. but evidence for using IgM enriched IVIg is even stronger,particularly in Gram Negative Sepsis[7]. IgM antibody preferentially bind to toxin in addition to bacterial antigen[8]. IgM is more potent in the septic process because of it's size which pursuits a more effective blocking of LPS(lipopolysaccharide) core on the bacterial surface. Earlier the IgM therapy is instituted,less likely will be Lipid- A induced tissue damage. IgM activates 100-400 times more complement than IgG and is more effective killer of bacteria.Opsonisation of bacteria by IgM is about 1000 times greater than IgG[9]. Specially in preterm VLBW&ELBW newborns who are deficient in IgG, IgM alters cell wall characteristics of antigen initiating its lysis or intracellular lysis after phagocytosis[10]. Several studies in India and abroad have shown IVIg therapy reduces the mortality and severity of sepsis in newborn. Very few studies have been done on role of IgM enriched IVIg in neonatal sepsis. We undertook the present study to evaluate the role of IgM enriched IVIg in the management of neonatal sepsis and its outcome.

MATERIALS AND METHOD

SETTINGS: After approval from Ethics Committee,our study was conducted over a period of 24 months in Special Newborn Care Unit and Baby Nursery of CNMCH, Kolkata.

STUDY PERIOD: 2 years(June 2016 to May 2018)

TYPE OF STUDY: It was a prospective,randomized study.

INCLUSION CRITERIA

All patients clinically presenting as sepsis. (both blood culture positive and negative cases were included)

EXCLUSION CRITERIA

Congentital anomalies of G.I, Respiratory system, CVS, CNS and other life threatening anomalies, Inborn errors of metabolism, severe perinatal asphyxia.

SAMPLE SIZE

We took 248 infants in each group(matched for gestational age, gender, weight and other variables). They were randomly allocated to receive antibiotic alone(control group) and antibiotics along with IgM enriched IvIg(immunotherapy group).

METHODOLOGY

Neonatal sepsis is not easy to define objectively.One or more of the following clinical features is suggestive of sepsis like lethargy, irritability, instability of temp>1^0 C, increased gastric aspirate with distended abdomen, hepatosplenomegaly, respiratorydistress (apnea, tachypnea, dyspnea, grunting), poorfeeding, vomiting, bradycardia/tachycardia, poor perfusion (CRT>3 sec.s), hypotonia, hypotension, icterus. Presence of any 2 or more of the following laboratory variables such as total Leucocyte count <5000/cumm, absolute neutrophil count <1500/cumm, band cells >20%, micro ESR >15mm in 1^{st} Hour, CRP>1 mg/dl suggest positive sepsis screen. When diagnosis is based onclinical and laboratory variables only, it is suspected sepsis. When blood and /or CSF culture is positive, it is proved sepsis. Perinatal risk factors are also important to suspect a case of Early Onset Sepsis (EOS).EOS (onset within first 72 hrs of life)is suspected if 2 or more of the following risk factors are positive- LBW babies<2500 gms or preterm babies <37 weeks gestation, febrile illness of mother within 2 weeks prior to delivery, foul smelling vaginal discharge and/or meconium stained amniotic fluid, prolonged rupture of membrane(PROM>24 hrs), more than 3 clean or single unclean P/V examination during first stage of labour, prolonged or difficult delivery with instrumentation, perinatal asphyxia (Apgar score <4 at 1 min) or difficult resuscitation. For each neonate enrolled in the study, all the records were noted down.

After selecting the newborns with clinically suspected sepsis, investigations planned and parental consent obtained. After collecting initial laboratory samples, babies of both groups were started i.v coamoxyclav 100mg/kg/day and amikacin 15 mg/kg/day. Other antibiotics were added or changed according to culture and sensitivity report obtained. Antibiotic therapy was continued for 14 days in case of "proved sepsis" (blood culture +ve) and 21 days in cases of meningitis (CSF culture +ve) and 5 to 7 days or more in cases of suspected sepsis. In addition to antibiotics and supportive treatment which was same in all the babies, immunotherapy group received IgM enriched IvIg 5ml/kg/day i.v. over 3-4 hrs in a day for 4 consequitive days.

RESULTS

248 infants in each group (i.e control group & immunotherapy group) who were comparable with regard to gestational age, sex, birth weight & other variables were selected.

Table-1: Bacteria isolated in blood culture(Fig .in parantheses indicate number of CSF culture +ve cases)

Bacteria isolated	Control group n=182(26)	Immunotherapy group n=192(34)
Klebsiella Pneumoniae	48(6)	56(8)
Coag negative Staph	34	44
E.Coli	36(12)	28(16)
Staph Aureus	20(2)	16
Enterococcus	8	12(2)
Enterobacter	10(2)	8
Pseudo aeruginosa	6	8
Citrobacter	10(4)	8(4)
Acinobacter	6	4
Salmonella	2	4(4)
Strep.viridans	2	4

Bold figure indicate common organism involved

Table 1 shows that commonest bacteria isolated from blood culture was Klebsiella pneumoniae and from CSF culture E.coli. In control group, 73.4%(182/248) were culture positive and rest 26.6% (66/248)were culture negative. In Immunotherapy group, 77.4%(192/248)were culture positive(proved sepsis)and rest 22.6% (56/248)were culture negative.

Table-2:Proved sepsis-Culture positive cases(fig.in parentheses indicate number of death)

VARIABLES	Control group n=182(70)	Death %	Immunotherapy group n=192(32)	Death %	P value
Early onset Sepsis(within 72 hours)	n=72(32)	44.4%	n=76(14)	18.4%	0.0007
<1000g	18(14)	77.8%	16(6)	37.5%	0.0189
1001-1500g	26(12)	45.2%	32(6)	18.8%	0.0315
1501-2500g	20(6)	30%	16(2)	12.5%	0.21259
>2500g	8(0)	0%	12(0)	0%	
Late onset Sepsis (after 72 hrs)	n=110(38)	34.5%	n=116(18)	15.5%	0.0010
<1000g	12(10)	83.3%	12(4)	33.3%	0.0150
1001-1500g	40(14)	35%	48(8)	16.7%	0.0497
1501-2500g	36(10)	27.8%	32(4)	12.5%	0.1222
>2500g	22(4)	18.2%	24 (2)	8.3%	0.3245

Table 2 shows the outcome in culture + ve cases. Out of 182 babies in the control group, 72 had EOS. Out of 192 babies in immunotherapy group76 had EOS. Death was more in ELBW, VLBW & LBW babies. In control group, death in ELBW was 77.8%(14/18),VLBW 45.1%(12/26) and LBW 30%(6/20) whereas in immunotherapy group death was 37.5%(6/18), 18.8% (6/32)and 12.5% (2/16) respectively. It clearly shows death was much less in immunotherapy group and it was satistically significant(p vaiue<0.001).p value was calculated by Med Calc's statistical software. In control group 110 babies had LOS and in immunotherapy group it was 116.Death was more in ELBW, VLBW and LBW babies. In control group death in ELBW was 83.3 % (10/12), VLBW 35%(14/40), LBW 27.8%(10/36) and normal birth weight 18.2 %(4/22) whereas in immunotherapy group, death was 33.3 %(4/12),16.7 %(8/48),12.5%(4/32) and 8.3 %(2/24) respectively. Here also death was much less in immunotherapy group compared to control group and it was satistically significant. (p value=0.0007).

Table-3: Suspected Sepsis-Culture Negative Cases(Fig.in paranthesis indicate number of deaths)

Variables	Control group n=66(18)	Death in %	Immunotherapy n=56(8)	Death in %	P value
Early onset Sepsis(within 72 hours)	N=22(12)	54.5%	N=18(6)	33.3%	0.1855
<1000g	4(4)	100%	4(2)	50%	0.1266
1001-1500g	10(6)	60%	6(2)	33.3%	0.3167
1501-2500g	4(2)	50%	6(2)	33.3%	0.6163
>2500g	4(0)	0%	2(0)	0%	-
Late onset sepsis (after 72 hours)	N=44(6)	13.6%	N=38(2)	5.2%	0.2029
<1000g	8(4)	50%	6(2)	33.3%	0.5471
1001-1500g	18(4)	11.1%	14(0)	0%	-
1501-2500g	12(0)	0%	14(0)	0%	-
>2500g	6(0)	0%	4(0)	0%	-

Table 3 shows the outcome in culture –ve cases. Out of 66 babies in control group, group, 22 had EOS & 44 had LOS. In Immunotherapy group,out of 56 babies, 18 had EOS and 38 had LOS. In EOS, death in control group was 100% (4/4) in ELBW, 60% (6/10) in VLBW and 50% (2/4) in LBW. Whereas in immunotherapy group it was 50%(2/4), 33.3%(2/6) and 33.3% (2/6) respectively. In LOS, death in control group was 50% (4/8) in ELBW and 11.1% (4/18) in VLBW whereas in immunotherapy group it was 33.3% (2/6) and 0 %(0/14)respectively.

Table-4: Comparison of death in two groups(fig.in parantheses indicate number of deaths)

Sepsis type	Control group n=248	Immunotherapy group n=248	p value
Proved Sepsis (Culture Positive)	70/182(38.5%)	32/192(16.6%)	0.0001
Suspected Sepsis(Culture Negative)	18/66(27.3%)	8/56(14.2%)	0.079
Overall (Proven + Suspected)	88/248(35.5%)	40//248(16.1%)	0.0001

Overall mortality in control group was 35.5% of which death in proved sepsis was 38.5% and in suspected sepsis was 27.3%.In immunotherapy group, overall death was 16.1% of which death in proved sepsis was 16.6 % and in suspected sepsis was 14.2%. So, in control group death rate was more than double both in proved and overall sepsis. It was satistically significant(pvalue<0.001). Most commn organism responsible for death in both groups was Klebsiella pneumoniae.

DISCUSSION

This study shows that IgM enriched IVIg is effective in reducing mortality in ELBW and VLBW infants with proven sepsis. Biological background of IgM supports it's efficiency. It is more efficient in

complement activation, better opsonisation, greater neutralization of both bacterial antigen and toxin all possibly due to it's pentameric structure[11]. This biological status of IgM together with our study's result will indicate to use it in VLBW and ELBW infants with culture positive sepsis. Similiar studies done by Cappsol *et al*. showed similar efficiancy of IgM enriched IVIg in VLBW babies with culture positive neonatal sepsis[12,13]. In a randomized trial of 60 Saudi septic neonates of various gestational ages, Haque et al showed that IgM enriched IVIg significantly decreased total neonatal mortality[14].

In a separate cohort study done by Haque et al on 195 neonates showed that IgM enriched IVIg is more effective than standard IVIg in decreasing neonatal mortality[15]. These reports do not clearly indicate their sepsis rate prevalance, making their results hard to compare.With a larger population study we detect a clinically relevant difference focusing only on the most suspectible babies (VLBW, ELBW).We show an effect of IgM enriched IVIg on mortality of those babies who had culture proven sepsis.Capassol *et al*. studied similiarly on VLBW infants with proven sepsis[12,13]. Like the Haque series[14,15], the most prevalent pathogens in our study were K.Pneumoniae & E.Coli on which IgM enriched IVIg works better. Anna Norby Teglind conducted a systemic review and meta analysis on the use of IgM enrinched IVIg in severe sepsis in pediatric and neonatal patients and found that it significantly reduced mortality in sepsis[16]. Despite encouraging results our study had some limitataions like it was observational in nature and focused strictly on short term mortality.

CONCLUSION

If we are to succeed in improving the outcome of neonatal sepsis, in addition to antibiotics, we should also modulate the immune system to recognise immune homeostasis. Based on our study, we conclude that immunomodulation by IgM enriched IVIg is effective in management of neonatal sepsis especially in culture positive cases of ELBW and VLBW babies.

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