

Better Developmental function at 3 years for infants born at 22-23wks who participated in the Randomized Controlled Trial for the Prevention of Intraventricular Hemorrhage by Indomethacin in Japanese Extremely Low Birthweight Infants

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Has documented that he/she has no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.

Indomethacin Trial

【Subjects】

To fulfill all of the following;

- Birth weight: 400g-999g
- Gestation: 22 weeks 0 day \leq
- 24 weeks \leq & birth weight standard deviation $-2.0 <$

【Method】

- Starting within 6 hours of birth 3 doses of IND or placebo were given with 6 hours continuous i.v. infusion every 24 hours.
- IND was given at the dose of 0.1 mg/kg-wt/dose.

【Outcomes】

Primary : IVH Grade III or IV within 7days

Secondary : Cerebral palsy, DQ at 3 year of age

718 infants assessed for eligibility

50 : Excluded
67 : Not approached

601 infants eligible

132 : No consent

469 infants

Stratified factors
Institution
G.W
Sex
In- / Out-born
Apgar at 1min

235 IND

Death : 22
Drop out, No data : 22

191

378 / 418
(90.4%)

234 placebo

Death : 29
Drop out, No data : 18

187

IVH Grade III or IV within 7days

IND	Placebo
16 / 235 (6.8%)	32 / 234 (13.7%)

odds ratio (95% CI) 0.37 (0.18-0.77)

effective to prevent severe Intraventricular hemorrhage (IVH)

(2005 SPR)

Cerebral palsy and/or Death around 3 years

	IND	Placebo
	odds ratio (95% CI)	
Death	22/235 (9%)	29/234 (12.4%)
	0.75 (0.4-1.4)	
Cerebral Palsy	31/235 (13.2%)	32/234 (13.7%)
	0.95 (0.54-1.69)	
Cerebral Palsy or Death	53/235 (22.5%)	61/234 (26.0%)
	0.82 (0.53-1.29)	

did not reduce the incidence of CP and/or Death

(2008 SPR/ASPR)

Incidence of IVH Grede III or IV and "CP or Death " stratified by Birth weight group

	IVH III or IV		CP or Death	
	IND	Placebo	IND	Placebo
	Odds ratio(95% CI)		Odds ratio(95% CI)	
400-599g	2/22	11/27	7/22	18/27
	0.14 (0.01-0.84)		0.23 (0.05-0.89)	
600-899g	12/164	19/150	39/164	34/150
	0.58 (0.25-1.32)		1.06 (0.60-1.86)	
900-999g	2/49	2/57	7/49	9/57
	1.17 (0.08-16.7)		0.88 (0.25-2.95)	

the incidence of "severe IVH" and "CP or death" significantly reduced in 400-599g

(2008 SPR/ASPR)

Stratified by gestational weeks

	IVH III or IV		CP or Death	
	IND	Placebo	IND	Placebo
	Odds ratio (95% CI)		Odds ratio (95% CI)	
22-23w	3 / 23	11 / 22	9 / 23	15 / 22
	0.15 (0.02-0.76)		0.3 (0.073-1.19)	
24-26w	13 / 136	24 / 135	35 / 136	39 / 135
	0.49 (0.22-1.06)		0.85 (0.48-1.51)	
27w-	1 / 76	2 / 76	9 / 76	7 / 77
	0.49 (0.01-9.71)		1.34 (0.42-4.50)	

Seem to be effective to reduce "severe IVH" and "CP or death" in 22-23wks

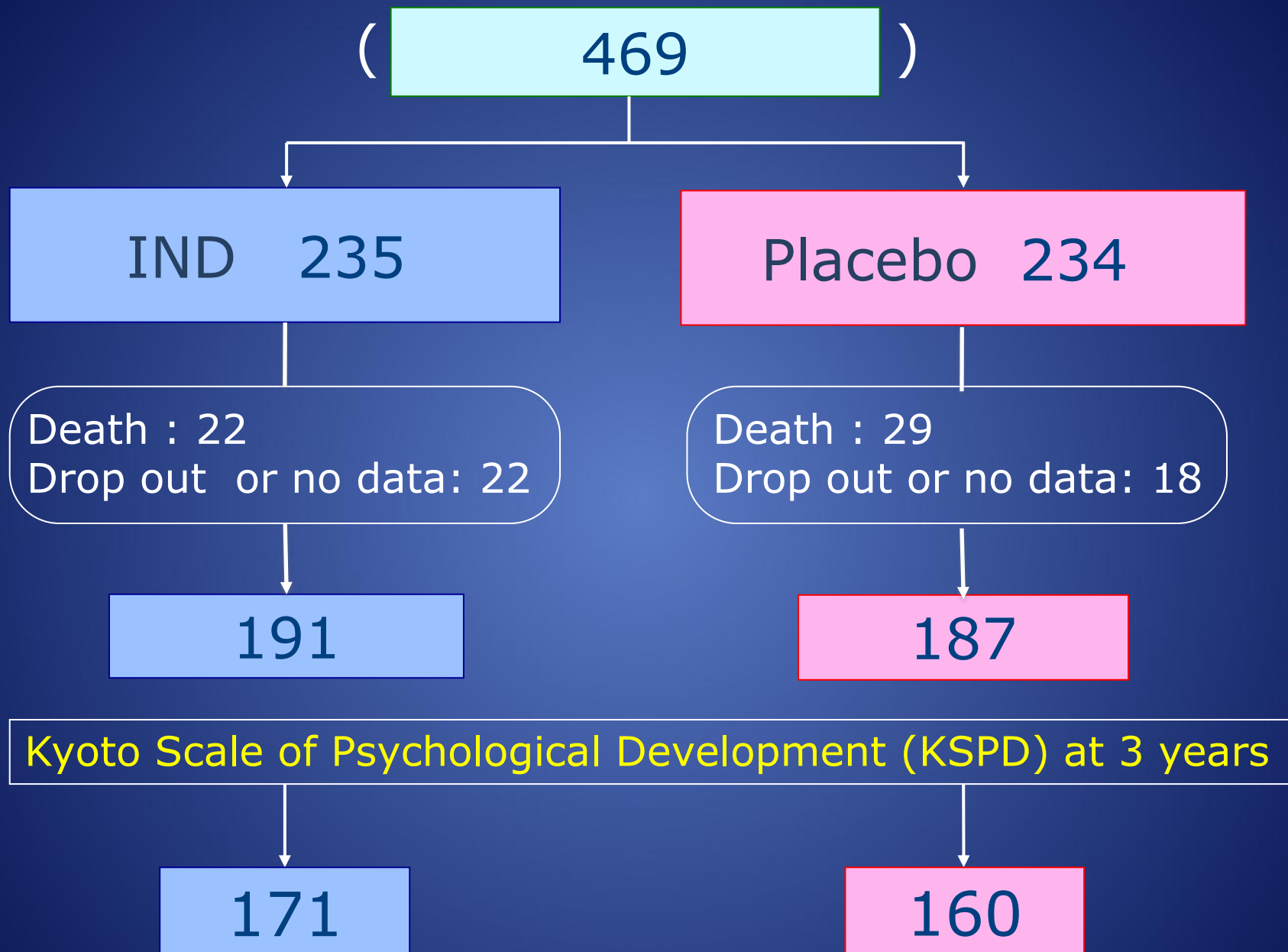
(2008 SPR/ASPR)

【 Objective 】

To compare the developmental quotient (DQ) using the Kyoto Scale of Psychological Development (KSPD) at 3 years between the two groups (IND or placebo) in follow-up study.

The KSPD (the kyoto scale of psychological development) :

- a standardized developmental function assessment tool for Japanese infants
- widely used at child counseling centers and at public health centers
- expressed as the developmental age (DA) for three areas
 - Cognitive-Adaptive (C-A)
 - Language-Social (L-S)
 - Postural-Motor (P-M)
 - Total score ; adding up for the three areas
- DQ: calculated dividing the DA by chronological age, then multiplied by 100



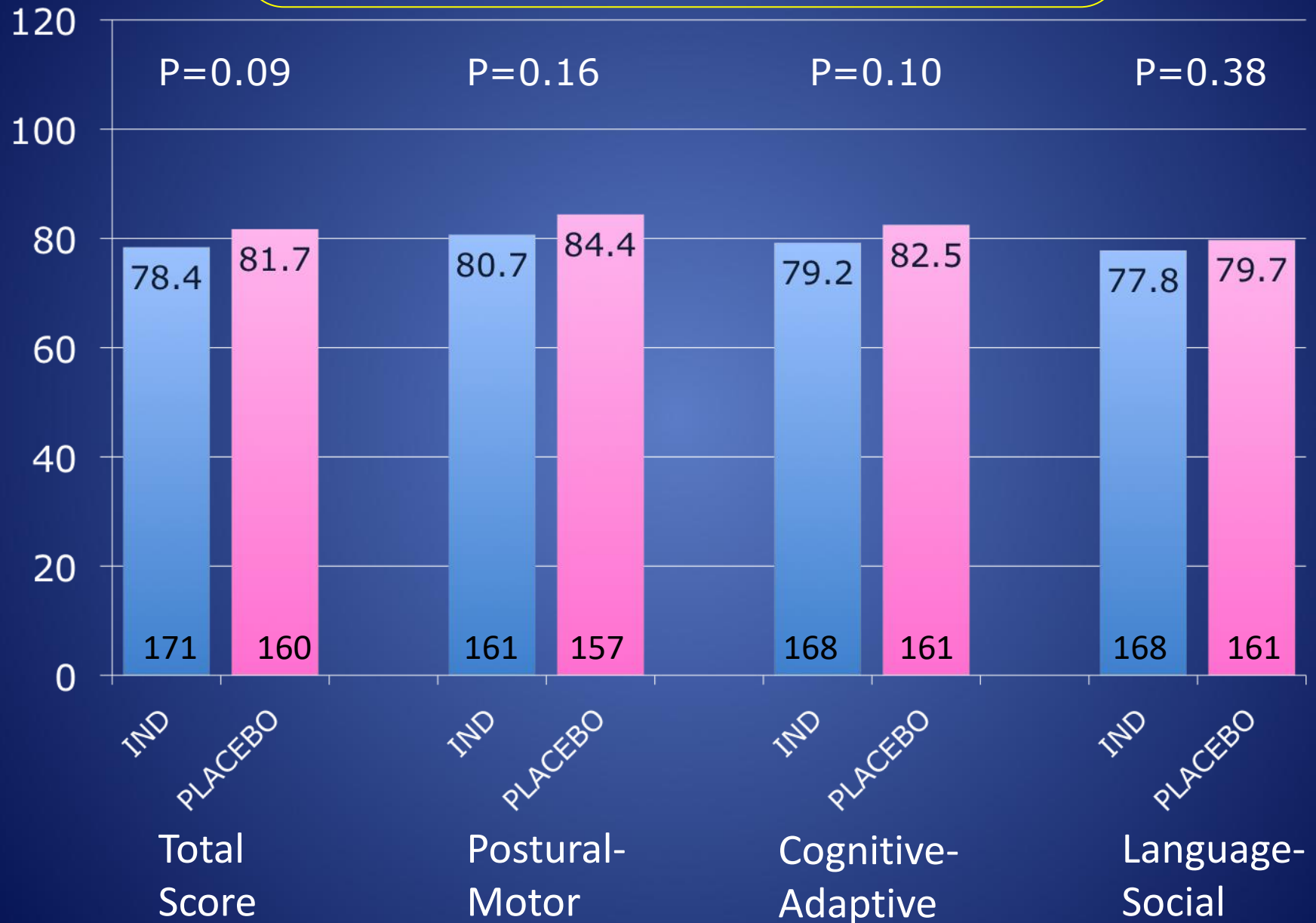
Baseline Characteristics 1

Mean \pm 1SD	IND (N=171)	Placebo (N=160)	<i>p</i>
Birthweight (g)	790.9 \pm 130.4	807.9 \pm 788.5	0.23
G.W.(w)	26.2 \pm 1.5	26.4 \pm 1.6	0.12
Apgar 5min	6.8 \pm 1.9	7.0 \pm 1.9	0.20
primipara	89 (52.1%)	77 (48.1%)	0.51
singleton	136 (79.5%)	122 (76.3%)	0.51
Vaginal delivery	42 (24.6%)	40 (25.0%)	1.0

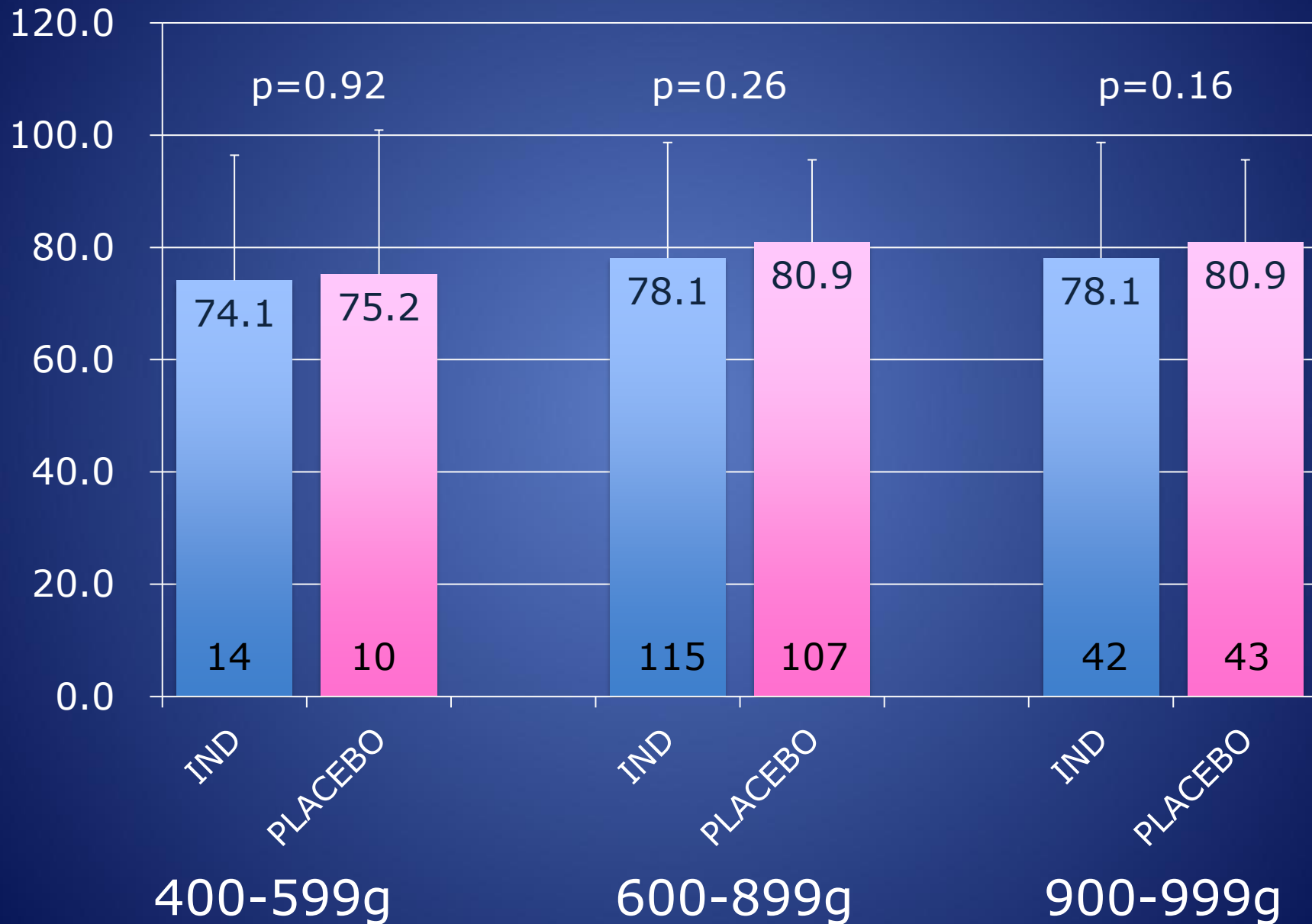
Baseline Characteristics 2

	IND (N=171)	Placebo (N=160)	<i>p</i>
Maternal steroid	79 (46.2%)	75 (46.9%)	0.78
Birth weight <-1.5 SD	24 (14.0%)	25 (15.6%)	0.75
RDS	133 (77.8%)	132 (82.5%)	0.34
Pneumothorax	3 (1.8%)	3 (1.9%)	1.0
IVH 3 or 4	12 (7.0%)	9 (5.6%)	0.65
CP	24 (14.0%)	19 (11.9%)	0.62

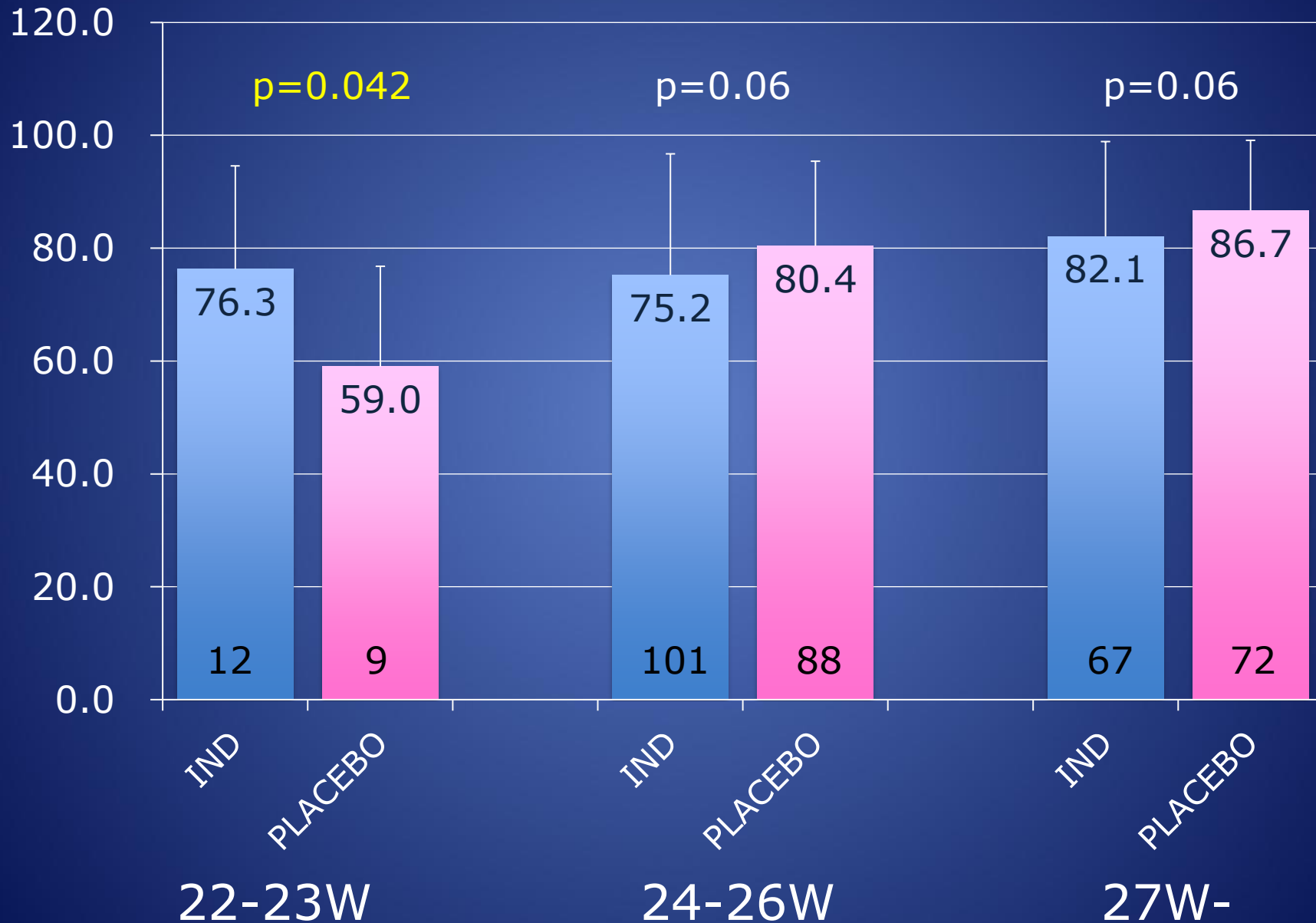
Comparison of KSPD -DQ



Comparison of Total Score DQ - by Birthweight group



Comparison of Total Score DQ -categorized by G.W.



22–23w Baseline Characteristics

Mean±SD	IND (N=12)	Placebo (N=9)	<i>p</i>
Birthweight (g)	598.3±90.0	574±102.9	0.57
Gestational Weeks(w)	23.3±0.37	23.2±0.45	0.43
Apgar 5min	6.3±1.5	6.4±2.1	0.80
primipara	6 (50%)	1 (11.1%)	0.16
singleton	11 (91.7%)	8 (88.9%)	1.0
Maternal steroid	3 (25%)	4 (44.4%)	0.40
RDS	10 (83.3%)	9 (100%)	
Male	5 (41.7%)	6 (66.6%)	0.39
IVH grade 3 or 4	1 (8.3%)	2 (22.2%)	0.55
CP	5 (41.7%)	4 (44.4%)	1.0

Conclusions:

1. There was no significant difference of DQ for all areas at 3 years evaluated by KSPD between IND and Placebo group in a large RCT in Japan.
2. In secondly analysis using the category of GW and Birthweight, DQ of IND group was significantly higher than that of Placebo group in 22-23GW group.
3. We have shown that Prophylactic use of indomethacin for prevention of IVH is effective in reducing CP and improving DQ for 22-23GW Japanese infants.