**Supplementary Material**

**Statistical Considerations**

The main goal of the study is to determine the benefit of higher dosage of indomethacin (HDI) compared with stopping treatment after the lower dosage (SDI).

The cascaded nature of the study, whereby patients only move to the higher dosing regimen if standard dosing does not close the PDA, complicates the analysis. The suggestion of potential selection bias is confirmed when we consider Table 1 in the manuscript where those on HDI have slightly lower gestational age (27.4 vs. 26.2, \( p = 0.01 \)) and birth weight (950 vs. 833 g, \( p = 0.05 \)). The overlapping group structure, SD vs. SD + HDI, leads to dependencies and therefore increased correlation that should also be considered in the analysis.

We performed a supplementary analysis to estimate the potential effect of selection bias on the analysis results by using propensity scores to create a case control setting. The 52 patients receiving HDI were considered as the treatment group, and the control group donor pool was defined to be those patients receiving standard dosing, excluding those patients that subsequently move to the HDI group (i.e., 248–52 = 196 patients).

We fitted a logistic model with dependent variable the indicator of treatment (SDI = 0, HDI = 1), and independent variables gender, birth weight and gestational age, to derive the score. We employed nearest neighbor 1:1 matching using the “MatchIt” package in R to find similar patients to those in the HDI group. Figure S1 shows the propensity scores of those matched compared with those unmatched; we can determine a good match between those paired in terms of their propensity score. Following matching, in the control group (SDI only) there were 42/52 primary PDA closures compared with 32/52 in the HDI group (81 vs. 62%, \( p = 0.05 \)). This supplementary analysis indicates a marginal trend toward the number of primary PDA closures being slightly higher in the standard dosing group compared with those receiving higher dosing; there had been random allocation of patients to each of the arms. Although this trend is marginally significant, it does not conclusively contradict the conclusion of no difference between the closure rates stated in the text of the article (section “secondary outcome: efficacy of treatment” (65.3 vs. 65.4%, \( p = 0.9 \)).

**Supplementary Figure S1** Matching in the control group (SDI only) versus treatment group (HDI).