Caffeine Auto-Wean Strategy in Premature Infants

Shabih Manzar, MD, MPH; Marissa K Johnston, PharmD, MPH

Abstract:

Objective: *There is a gap in the literature regarding the weaning plan of caffeine in stable, low-risk preterm infants. As a quality improvement initiative, this study aimed to decrease caffeine utilization and cost by following an auto-wean strategy.*

Methods: *We implemented a practice change by not adjusting the dose of caffeine after 32 weeks of postmenstrual age on stable, low-risk preterm infants. The staff was educated through protocol presentation and discussion through emails. The caffeine utilization and cost were calculated for 32 weeks (actual) and then for 34 weeks (predicted). The differences were obtained by subtracting the actual from the predicted dose.*

Results: *A total of sixteen infants were evaluated in the study period. The total actual utilization of caffeine was 10.64 mL, with a mean of 0.67 mL, while the total predicted utilization was 13.73 mL, with a mean of 0.86 mL, p = < 0.001. The total actual cost was $32.66, with a mean of $2.04, while the total predicted cost was $42.14, with a mean of $2.63, p = < 0.001. We noted a 22.4% reduction in caffeine utilization and 22.4% in cost.*

Conclusions: *We demonstrated effective auto-weaning of caffeine in stable, low-risk preterm infants. As this is a single institutional study, more studies are needed at other institutions to examine our findings' external validity.*

Abbreviations: GA, gestational age; PMA, postmenstrual age; IHI, Institute for Healthcare Improvement; IRB, Institutional Review Board; CF, conversion factor; IH, intermittent hypoxia

Keywords: Caffeine, preterm infants, cost, utilization, quality improvement, autowean

Introduction:

Caffeine is used in premature infants to treat apnea of prematurity. Generally, it is started at admission on all infants < 32 weeks gestational age (GA). For neonates between 32–34 weeks GA, caffeine is initiated per clinical symptoms or at the provider's discretion. There are no clear guidelines for when to discontinue caffeine. Most clinicians discontinue caffeine around 33–34 weeks postmenstrual age (PMA) or if the infant has been apnea-free for more than or equal to 5–7 days. (1,2) Although there is wide variability in the timing of caffeine discontinuation, caffeine is usually discontinued at 34 weeks PMA in our institution. (3) The current practice is to weight-adjust caffeine until discontinued. We do not monitor serum caffeine levels because concentrations are predictably within the therapeutic range when standard doses are given. (4,5)

"Caffeine is used in premature infants to treat apnea of prematurity. Generally, it is started at admission on all infants < 32 weeks gestational age (GA). For neonates between 32–34 weeks GA, caffeine is initiated per clinical symptoms or at the provider's discretion. There are no clear guidelines for when to discontinue caffeine. Most clinicians discontinue caffeine around 33–34 weeks postmenstrual age (PMA) or if the infant has been apnea-free for more than or equal to 5–7 days."

Caffeine clearance and volume of distribution are significantly influenced by postnatal age and current body weight. The half-life of caffeine citrate is 100 hours at birth and 5 hours at a GA >29 weeks. There is a remarkable shortening of the half-life during neonatal maturation. (6,7) Caffeine is rapidly absorbed with complete bioavailability; therefore, no dose adjustments are needed when switching from parenteral and oral doses. Caffeine has a broad therapeutic index in preterm newborns. A level of 2 mg/L has measurable efficacy on the respiratory drive. Caffeine competitively inhibits adenosine receptors (A1 and A2A) at these levels. (8)

Koch et al. suggested that the caffeine maintenance dose should be increased by 1 mg/kg every 1–2 weeks to ensure stable caffeine concentrations during the first eight weeks of life. (9) However, to date, there is no commonly agreed standardized protocol on dose adjustments and timing of caffeine. (10)

Caffeine use in preterm infants has been demonstrated to prevent bronchopulmonary dysplasia, improve survival without neurodevelopmental disability at 18–40 months, and improve motor function at 11 years. (11,12) Conversely, caffeine has been associated with a marked reduction of cerebral and intestinal blood flow, temporarily reduced weight gain, and an increase in episodes of tachycardia, reflux, and feeding intolerance. (11,13,14,15) It is, therefore, essential to attempt to wean caffeine in stable, low-risk preterm infants once they reach a certain gestational age.

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There is a gap in the literature regarding the weaning plan of caffeine in stable, low-risk preterm infants. As a quality improvement initiative, we planned this study to decrease caffeine utilization and cost by following an auto-wean strategy. The secondary aim is to see if caffeine auto-wean could be done successfully and safely.

Material and Methods:

The Institutional Review Board (IRB) approved this study. The protocol number was STUDY00002307. The need for consent was waived as data was collected as the standard of care. All infants received the same treatment. This study was conducted to improve healthcare quality by reducing cost and drug exposure to the patient. The rationale and specific aims were addressed per the SQUIRE 2.0 guidelines. (16) We implemented a practice change by not adjusting the dose of caffeine after 32 weeks of PMA on stable, low-risk preterm infants. The staff was educated through protocol presentation and discussion through emails. The concerns raised about the need for change were addressed, and a final agreement was reached to apply the change after the IRB approval. We used the quality improvement framework of the Institute for Healthcare Improvement (IHI) method of improvement using the SMART AIM. (17) The driver diagram is shown in Figure 1. The study was started on February 5, 2023 and completed on April 20, 2023.

Once the infant reached a PMA of 32 weeks, the caffeine dose was not weight-adjusted (Supplementary material, S1, Flow diagram chart). The number of apneic or desaturation episodes (> 3 from baseline) was monitored as a balancing measure. Apnea was defined as cessation of breathing for > 20 seconds. Significant desaturation was defined as saturation < 90 for > 5–10 seconds or need for intervention (stimulation or increase in FiO_2). (18)

The utilization was primarily assessed as the total milliliters (mL) of caffeine used. The cost was calculated for each mL used. In converting milligrams (mg) to mL, a conversion factor (CF) of 0.05 was used. The CF was obtained by deduction method (20 mg in 1 mL, so 1 mg = 1/20 = 0.05 mL). In converting the mL to cost ($), a conversion factor (CF) of 3.07 was obtained by the deduction method (oral caffeine is supplied as a 60 mg/3 mL [20 mg/mL] vial). A pack of 10 vials cost $92.12 ($9.21/vial); therefore, the cost per mL is $3.07 ($9.21/3 mL). The caffeine utilization and cost were calculated for 32 weeks PMA (actual) and then for 34 weeks PMA (predicted). The differences were obtained by subtracting the actual from the predicted dose. Microsoft Excel program was used for all calculations. Student t-test was used for comparison.

"Once the infant reached a PMA of 32 weeks, the caffeine dose was not weight-adjusted (see S1, Flow diagram chart). The number of apneic or desaturation episodes (> 3 from baseline) was monitored as a balancing measure. Apnea was defined as cessation of breathing for > 20 seconds. Significant desaturation was defined as saturation < 90 for > 5–10 seconds or need for intervention (stimulation or increase in FiO_2)."

Ethical Approval and Informed Consent:

The Institutional Review Board of Louisiana State University Health Sciences approved this study. The protocol number was STUDY00002307. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. The need for consent was waived as data was collected as the standard of care.

Results:

A total of sixteen infants were evaluated in the study period. The median birth weight was 835 grams (470 – 2350 grams). The median GA was 26 weeks (range 23 – 31weeks). The male-to-female ratio was 1:1. Out of sixteen, eleven infants were African American, four infants were White, and one infant was Hispanic. Table 1 displays the individual details of each infant. None of the infants had apnea or significant desaturation episodes during the two-week auto-wean observation period (32–34 weeks). One infant was excluded from the analysis as the caffeine dose was increased at 31 weeks by the on-call provider to 15 mg/kg/day for frequent desaturations. Later, it was found to be related to the dislodgment of the nasal cannula. Two infants were continued on caffeine until 35 weeks PMA at the provider's discretion. The dose per weight at 34 weeks PMA was used in those cases.

The total actual utilization of caffeine for 16 infants was 10.64 mL, with a mean of 0.67 mL, while the total predicted utilization was 13.73 mL, with a mean of 0.86 mL, p = < 0.001. The total actual cost was $32.66, with a mean of $2.04, while the total predicted cost was $42.14, with a mean of $2.63, p = < 0.001. We noted a 22.4% reduction in caffeine utilization (Figure 2A) and 22.4% in cost (Figure 2B).

Discussion:

The study was aimed primarily at reducing caffeine utilization by

Figure 2A: Graph showing a 22.48 % reduction in Caffeine (mL) use.

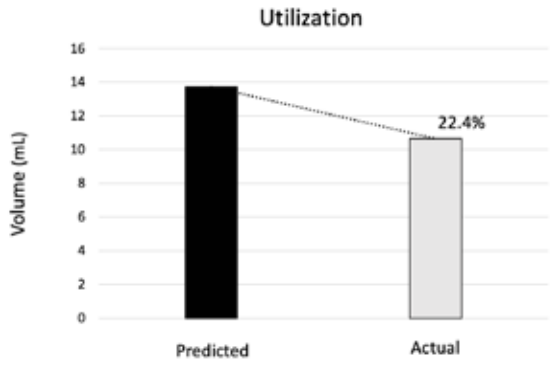
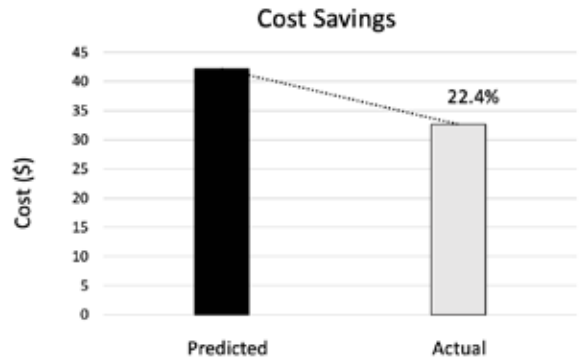


Figure 2B: Graph showing a 22.48% reduction in the cost ($) of Caffeine.



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10%. We demonstrated a reduction of 22.4% without any clinical change in the status of the infants related to caffeine. A significant reduction in medication utilization supported the concept of value-based care (i.e., quality of health outcomes per dollar spent). (18,19) We also observed a cost reduction of 22.4%. Although caffeine is not an expensive medication in terms of total dollars, the magnitude of cost savings noted in the study was substantial.

"The study was aimed primarily at reducing caffeine utilization by 10%. We demonstrated a reduction of 22.4% without any clinical change in the status of the infants related to caffeine. A significant reduction in medication utilization supported the concept of value-based care (i.e., quality of health outcomes per dollar spent). (18,19) We also observed a cost reduction of 22.4%. Although caffeine is not an expensive medication in terms of total dollars, the magnitude of cost savings noted in the study was substantial."

There have been concerns raised about intermittent hypoxia (IH) and the possible role of caffeine beyond 34 weeks PMA. Recently, Rhein et al. suggested prolonged caffeine use to prevent IH after 34 weeks PMA. (20) They used an oral maintenance dosage of 6 mg/kg/day. Oliphant et al. studied the effect of caffeine on the rate of reduction of IH among late-preterm infants. (21) They reported that 10 mg/kg/day and 15 mg/kg/day doses significantly lower the incidence of IH. They did not find 15 mg/kg/day as effective as 10 mg/kg/day, suggesting a non-dose-dependent response. Also, infants in the placebo group were clinically asymptomatic. Recently, Conlon et al. suggested that a dose of > 6 mg/kg/day effectively decreases IH in preterm infants, questioning over-treating. (22) As noted in the study, even without weight adjustment, each patient's caffeine dose was greater than the minimum dose of 6 mg/kg/day associated with IH (Supplementary material, Table S2).

The study limitation was a small sample size. As this is a quality improvement project, we will continue to perform plan-do-study-act cycles to see the sustained improvement observed in the current study. One could argue that not adjusting the caffeine dose to weight change may lower the serum caffeine level and lead to clinical symptoms. None of the infants had any clinical issues related to the dose of caffeine non-adjustment. We did not measure the serum caffeine level in any infants because concentrations are predictably within the therapeutic range when standard doses are given. (4,5) We used 10 mg/kg/day as a maintenance dose. As noted in the study, the final dose each infant received during the weaning period (32–34 weeks PMA) was greater than 6 mg/kg/day, which should be adequate to prevent IH. The study's strength

Figure 1. The Driver diagram

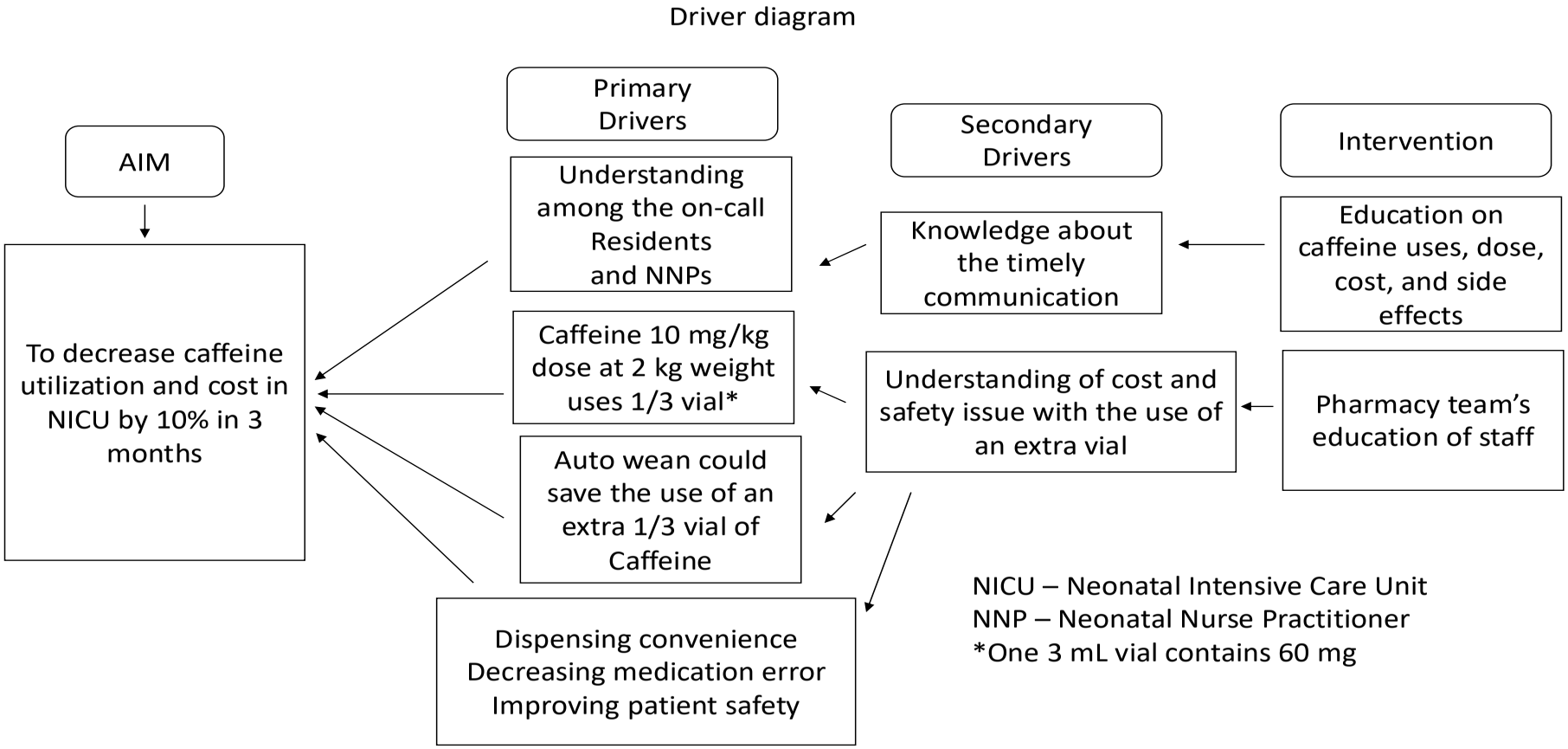


Table 1: Summary of The Findings

Case no	Birth weight	GA	Sex	Race	Weight at 32 weeks (kg)	Caffeine dose (mg) at 32 weeks	Caffeine dose (mg per kg) [dose/wt]	Actual ml [dose x 0.05 CF]	Weight (kg) at 34 weeks	Caffeine expected 10 mg/kg dose at 34 weeks	Predicted mL [dose x 0.05 CF]	Difference in mL [predicted – actual]	Cost $ (conversion factor) 3.07 for PO [ml x 3.07]
Case 1	1.100	27.0	F	W	2.000	17.2	8.60	0.86	2.520	25.2	1.26	0.40	1.22
Case 2	1.680	31.5	M	W	1.590	16.8	10.57	0.84	2.005	20.05	1.00	0.16	0.50
Case 3	1.250	31.4	F	B	1.200	12.6	10.50	0.63	1.355	13.55	0.68	0.05	0.15
Case 4	0.470	23.6	F	B	1.070	8.6	8.04	0.43	1.360	13.6	0.68	0.25	0.77
Case 5	2.350	31.5	M	H	2.330	23.6	10.13	1.18	2.430	24.3	1.22	0.03	0.11
Case 6	1.280	30.1	F	B	1.318	12.8	9.71	0.64	1.830	18.3	0.92	0.28	0.84
Case 7	0.870	30.1	F	B	0.915	9.6	10.49	0.48	1.250	12.5	0.63	0.15	0.44
Case 8	0.670	26.6	M	B	1.125	10.8	9.60	0.54	1.380	13.8	0.69	0.15	0.46
Case 9	0.685	23.6	M	B	1.345	13.4	9.96	0.67	1.705	17.05	0.85	0.18	0.56
Case 10	0.550	26.0	F	B	1.165	11.2	9.61	0.56	1.410	14.1	0.71	0.15	0.44
Case 11	0.800	25.6	M	B	1.755	16.8	9.57	0.84	2.130	21.3	1.07	0.23	0.69
Case 12	0.670	25.5	F	B	1.240	12.2	9.84	0.61	1.530	15.3	0.77	0.16	0.47
Case 13	1.005	28.2	F	B	1.285	12	9.34	0.60	1.760	17.6	0.88	0.28	0.86
Case 14	0.545	26.5	M	W	1.195	10.2	8.54	0.51	1.450	14.5	0.73	0.22	0.66
Case 15	0.755	26.5	M	W	1.320	13	9.85	0.65	1.640	16.4	0.82	0.17	0.52
Case 16	1.035	30.0	M	B	1.280	12	9.38	0.60	1.695	17	0.85	0.25	0.77

Footnote for the Table:

GA: Gestational age in weeks

BW: Birth weight, expressed in kilograms.

The mg to mL Conversion Factor (CF) of 0.05 was obtained from:

20 mg in 1 mL

1 mg = 1/20 = 0.05 mL

Actual dose (mL) = Caffeine dose at 32 weeks x 0.05 (CF)

Predicted dose (mL) = Caffeine dose expected at 34 weeks (if adjusted for weight at 10 mg/kg) x 0.05 (CF)

The mL to cost ($) Conversion Factor (CF) of 3.07 was obtained from:

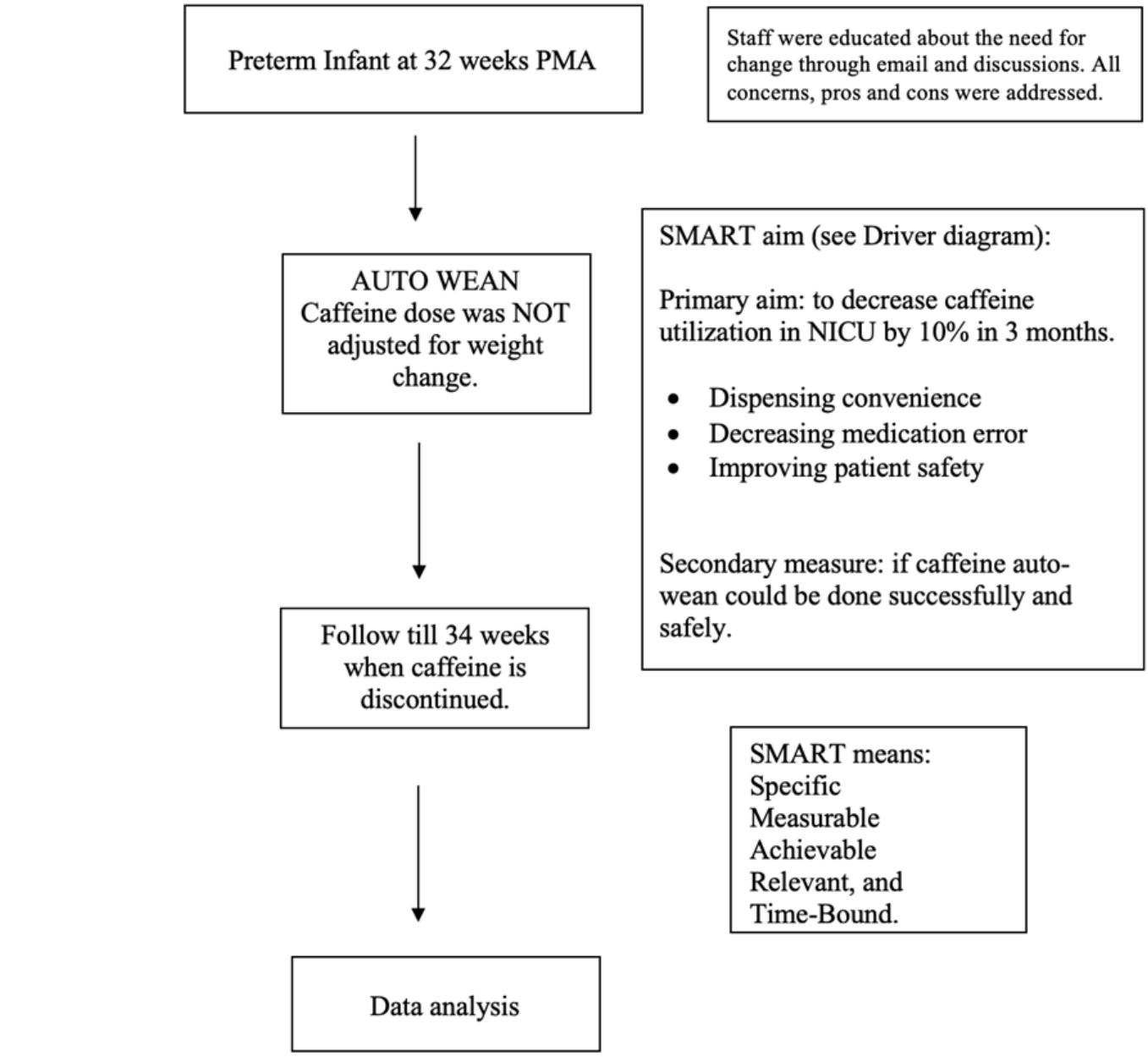
Oral Caffeine is supplied as 20mg/mL in 3mL Vials. The cost is $92.12/Pack of 10

So, one vial would be $9.21 ($92.12 divided by 10)

Cost per vial of 3 mL =$9.2 or $3.07 per mL ($9.21 divided by 3)

Appendix A

CAFFEINE AUTO WEAN STUDY
Study Flow Diagram



Balancing factors:
Number of apneic episodes (apnea > 20 seconds)
Desaturations < 90% (> 5-10 seconds, requiring stimulation or increase oxygen/flow)

as a quality improvement project was achieving the preset aim of a change in the process resulting in decreased resource utilization and cost within the three-month period.

"One could argue that not adjusting the caffeine dose to weight change may lower the serum caffeine level and lead to clinical symptoms. None of the infants had any clinical issues related to the dose of caffeine non-adjustment."

Conclusion:

We demonstrated effective auto-weaning of caffeine in stable, low-risk preterm infants. This being a single institutional study, more such studies are needed at other institutions to examine our findings' external validity.

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Supplementary Material (Table S2)

Appendix B: Actual dose at 34 weeks (dose/weight)

Caffeine dose (mg) at 32 weeks	Weight (kg) at 34 weeks	Actual Final dose at 34 weeks (mg/kg)
17.2	2.520	6.8
16.8	2.005	8.4
12.6	1.355	9.3
8.6	1.360	6.3
23.6	2.430	9.7
12.8	1.830	7.0
9.6	1.250	7.7
10.8	1.380	7.8
13.4	1.705	7.9
11.2	1.410	7.9
16.8	2.130	7.9
12.2	1.530	8.0
12	1.760	6.8
10.2	1.450	7.0
13	1.640	7.9
12	1.695	7.1

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