Model-Based Meta-Analysis of Paracetamol Dose-Response in Paediatric Tonsillectomy Pain

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Introduction and Objectives

- Developing medicines for children is challenging due to **ethical constraints** and **limited clinical data**.
- Traditional paediatric trials are often **slow**, **costly**, and **difficult to conduct**.
- Modelling and Simulation techniques, **particularly Model-Based Meta-Analysis (MBMA)**, integrate data from multiple studies to **predict drug behaviour**, and **optimise dosing** [1].
- MBMA has the potential to minimise the need for paediatric trials and supports **safer** and **faster treatment access**.

Objectives:

- Identify a postoperative pain indication with both **adult** and **paediatric data** (shared endpoints/treatments).
- Curate a **paediatric analysis dataset** focusing on one treatment only as a **proof-of-concept study.**
- Develop an **MBMA framework** to characterise treatment response in paediatric patients.

Study Identification Workflow

- Study selection and reporting were conducted in accordance with the **PRISMA statement** [2], as shown in Fig. 1:

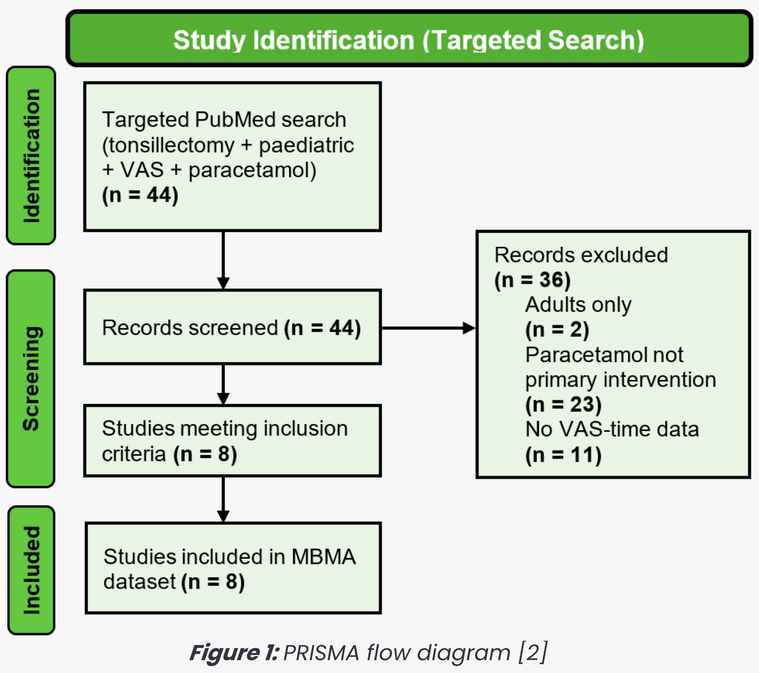

Figure 1: *PRISMA flow diagram [2]*

Dataset Summary

- Aggregated-level time-pain score data were extracted from eight publications [3-10] and curated into the **MBMA dataset**.
- Studies: **8** (paediatric tonsillectomy)
- Intervention drug: Paracetamol
- Outcome: **Visual Analogue Scale (VAS)** pain score, which measures pain on a scale from 0 to 100 mm (Fig. 2: 0 = no pain, 100 = worst possible pain)

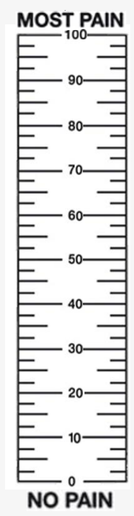

Figure 2: *VAS scale*

Summary of Treatment Arms

- Doses were standardised as shown in Table 1.

Study/Arm	N	Standardised Dose	Route
Alper Y – Arm 1	25	**0.0132**	IN (Intranasal)
Alper Y – Arm 2	25	**40**	IV (Intravenous)
Jotic A – Arm 1	92	**12.5**	NR (Not Reported)
Sener M – Arm 1	40	**16.5**	IV
Sener M – Arm 2	40	**14**	IV/Control
Soltani R – Arm 1	24	**12.5**	Oral
Dashti G – Arm 1	53	**40**	Rectal
Dashti G – Arm 2	51	**0**	NR/Control
Hamers J – Arm 1	83	**40**	NR
Hamers J – Arm 2	28	**40**	NR
Uysal H – Arm 1	32	**15**	IV
Ozlugedik S – Arm 1	27	**15**	NR

Table 1: *Summary of included treatment arms (Dose standardised to mg/kg/day)*

Note: Hamers J arms reflect different clinical indications [adenoidectomy & (adeno)tonsillectomy]

MBMA Modelling

- Two MBMA models were developed with an aim to describe **time-response** and **dose-response** relationships.
- To evaluate model robustness, the following strategy was employed (Fig. 3):

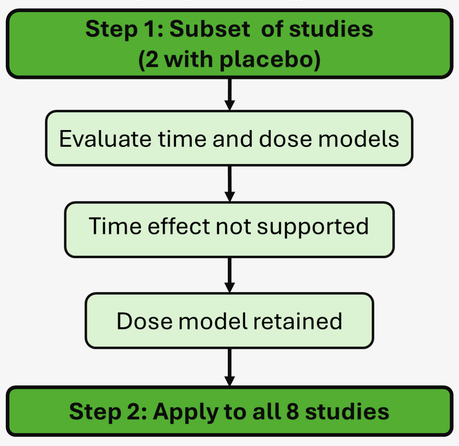

Figure 3: *Modelling strategy for MBMA*

Dose-response model (Emax):

$$y_o = 100 \cdot invlogit\left(pbo.eff_t - \frac{Emax \cdot dose}{dose + ED50}\right)$$

Here:

y_o: Predicted pain response (%), $pbo.eff_t$: Baseline placebo effect at time t (%), t: Post-operative time at which pain observations were recorded (h), $dose$: Administered paracetamol dose (mg/kg/day), $Emax$: Maximum treatment effect (no units), $ED50$: Dose leading to 50% of the maximum effect (mg/kg/day)

Model Results

- Population parameter estimation analysis was conducted in **R Studio**, employing the **Generalised Nonlinear Least Squares (GNLS) algorithm** [11], yielding the following dose-response parameter estimates, summarised in Table 2:

Model & Dataset	Model Parameters (units)	Pop. Value	Std. Error	AIC	BIC
Emax model 2 studies [3-4]	E_{max} (no units)	1.228	1.28	139.28	154.56
	ED_{50} $(mg/kg/day)$	23.23	2.03		
Emax model 8 studies [3-10]	E_{max} (no units)	1.023	1.94	512.99	667.62
	ED_{50} $(mg/kg/day)$	43.51	3.14		

Table 2: *Summary of estimated dose-response parameters along with statistical metrics*

Model Evaluation

- Model evaluation was performed using goodness-of-fit plots, e.g., as shown in Fig. 4:

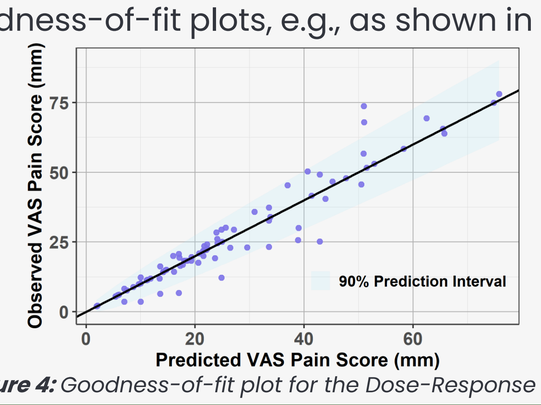

Figure 4: *Goodness-of-fit plot for the Dose-Response model*

Model Fits

- Paediatric tonsillectomy pain data analysed for paracetamol and placebo treatment groups, with corresponding GNLS model fits in Fig. 5.

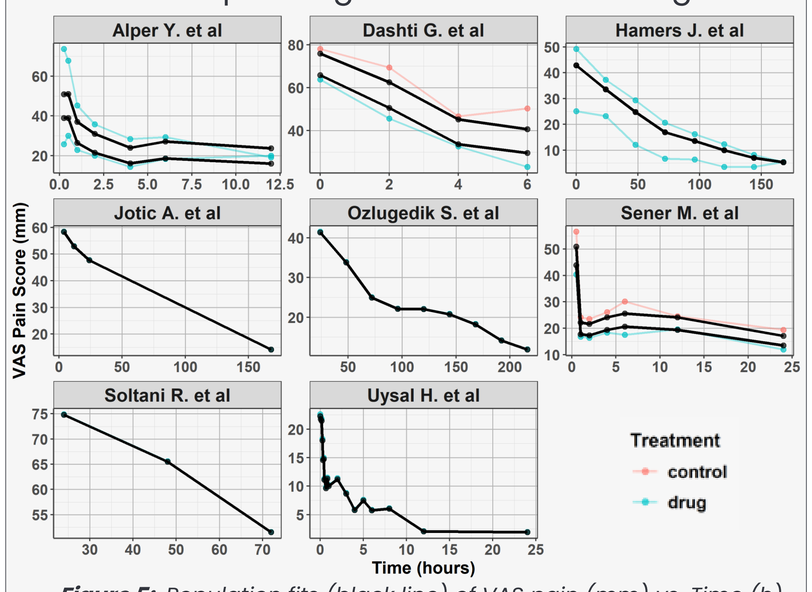

Figure 5: *Population fits (black line) of VAS pain (mm) vs. Time (h) for all studies*

Covariate Exploration

- **Rescue therapy** was explored as a **covariate** but was not supported by the data (Fig. 6).
- **Background therapy** could not be evaluated due to no between-study variability (0% or 100% use), and the **route of administration** was also not supported.

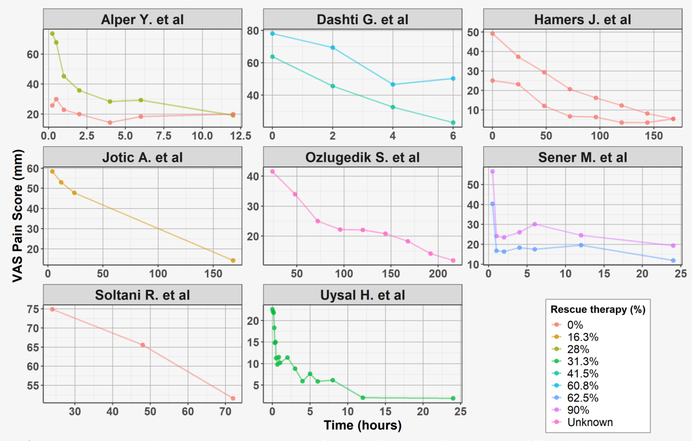

Figure 6: *Exploratory VAS pain trajectories stratified by treatment arms and rescue therapy across studies*

Conclusions and Future Work

- An MBMA framework has been successfully developed to characterise **paracetamol dose-response** in paediatric tonsillectomy pain.
- There is **no evidence** of a **time-dependent effect** based on available aggregated data.
- The **Emax model** adequately described the observed dose-response relationship.
- Future work: 1) Expand the dataset with adult studies to assess **MBMA extrapolation** and 2) Explore applicability across **drug classes** and **pain scale definitions.**

References

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