

### Heparin flushing of IV lines

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### Executive Summary

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#### Background

Monash Health are working on improving procedural and maintenance documentation as a result of the dramatic increase in the size of the lines service with the opening of the new Children's Hospital. As part of this, they are re-considering the use of heparin for flushing paediatric lines which is common practice around the world.

Changing practice from heparin to saline at Monash Health would be a significant change in practice. Anaesthetics have engaged the Centre for Clinical Effectiveness to undertake a rapid review of current literature about the use of heparin for flushing paediatric lines.

#### Objective

The purpose of this Rapid Review was to synthesise recent evidence pertaining to the use of heparin versus saline flushing of peripheral lines to maintain patency in paediatric patients.

#### Search Strategy

Databases searched were Pubmed, CINAHL and TRIP from 2012 to current. Searches were conducted by one author (CJ) and exported to Endnote X7. From there, titles and abstracts were screened (CJ). Papers identified were screened using inclusion and exclusion criteria established *a priori*.

#### Results

The search of the literature identified one systematic review (Kumar et al, 2013), one scoping review (Takashima et al, 2015) and one RCT (Upadhyay et al, 2015), all of high methodological quality. The quality of included primary studies in Kumar (2013) systematic review indicated a varied quality.

The Centre for Clinical Effectiveness undertook a meta-analysis of results for catheter patency from Kumar et al (2013) and Upadhyay et al (2015). The definition of patency and functional duration used in both Kumar and Upadhyay refers to the duration of time the catheters were in place. The meta-analysis of catheter patency from Kumar et al (2013) and Upadhyay et al (2015) indicates that for heparin usage as an intermittent flush solution, there is a smaller benefit, mean difference= 3.88 hours (95% CI 0.23 to 7.52).

The most common reported dose of heparin was 10 units/mL (Kumar et al 2013).

No significant differences were found between heparin and saline for occlusion incidence, line failure/infusion failure, phlebitis or adverse events such as heparin-induced thrombocytopenia (HIT) or sepsis.

#### Conclusions

In conclusion, this review of evidence found in favour of heparin for the reduction in incidence of IV blockages/catheter patency in paediatric populations requiring intermittent flushing of peripherally inserted lines. The results did not show any statistically significant benefit for heparin versus saline for outcomes related to occlusion incidence, line failure, phlebitis or other adverse events.

## Background

Monash Health are working on improving procedural and maintenance documentation as a result of the dramatic increase in the size of the lines service with the opening of the new Children's Hospital. As part of this, they are re-considering the use of heparin for flushing paediatric lines which is common practice around the world, however recent evidence has suggested that using heparin over saline does not show any significant difference in the line blockage incidence.

Changing practice from heparin to saline at Monash Health would be a significant change in practice. Anaesthetics have engaged the Centre for Clinical Effectiveness to undertake a rapid review of current literature.

## Objectives

The purpose of this Rapid Review was to synthesise recent evidence pertaining to the use of heparin versus saline flushing of peripheral lines to maintain patency in paediatric patients.

## Search strategy

### Search strategy

Search terms were taken and adapted to capture the paediatric setting from a recent Cochrane Review (Bradford et al, 2015.) (Appendix 1, Table 1). Databases searched were Pubmed, CINAHL and TRIP from 2012 to current. Searches were conducted by one author (CJ) and exported to Endnote X7 (Thompson, Reuters, Carlsbad, California, USA. From there, titles and abstracts were screened (CJ). Papers identified were screened using inclusion and exclusion criteria established *a priori*.

### Inclusion/Exclusion Criteria

Inclusion/exclusion criteria can be found in Table 2.

**Table 2.** Inclusion/Exclusion criteria

|                          |  |
|--------------------------|--|
| <b>Population</b>        | <b>Include:</b> Paediatric (includes Neonates), child, adolescent (<18 years)<br><b>Exclude:</b> Adult (>18 years)   |
| <b>Interventions</b>     | <b>Include:</b> Heparin flushing of any concentration  |
| <b>Control</b>           | <b>Include:</b> Saline or 9% sodium chloride solution  |
| <b>Outcomes</b>          | <b>Include:</b> IV line blockage/catheter patency; occlusion incidence; line failure/infusion failure; Phlebitis   |
| <b>Types of evidence</b> | <b>Include:</b> Systematic reviews and RCTs only<br><b>Exclude:</b> Observational studies, qualitative studies, editorials, opinion pieces, grey literature, case studies. |
| <b>Limits</b>            | <b>Date:</b> 2012 onwards<br><b>Language:</b> Publications in English.   |

### Quality Appraisal

Standard quality appraisal criteria were used to assess the methodological quality of the included papers.

## Results

The search of Pubmed, CINAHL and TRIP identified 76 results after accounting for duplicates. Abstract and full text were screened and based on inclusion criteria. One systematic review (Kumar et al, 2013), one scoping review (Takashima et al, 2015) and one RCT (Upadhyay et al, 2015), which was published after the Kumar (2013) systematic review, were included. A summary of these papers is presented in Table 3.

### Summary of Findings

#### *IV line blockage/catheter patency*

For heparin usage as an intermittent flush solution Kumar et al (2013) reported a pooled estimate from the available RCTs showing a small benefit (MD, mean difference: 2.82 hours; 95% CI: 20.04 to 5.67; P = .05), with no significant difference in effect size noted between the studies restricted to the neonatal population and the other studies who

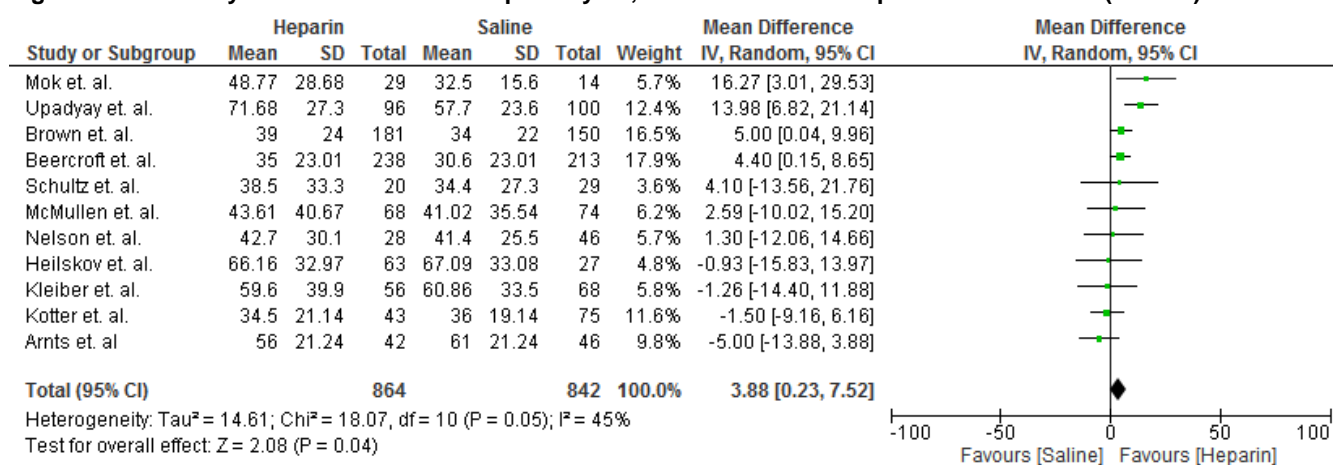
combined neonates with infants and children above the age of one year old. There was no significant heterogeneity noted in the estimates from these trials.

The most common dose of heparin used in studies reported in Kumar et al (2013) was 10 units/mL, although there was minimal additional benefit observed when this dosage was compared with the lower dosage, within-study design of 2 multi-group studies.

Upadhyay et al (2015) reported mean functional duration of first catheter was longer in heparinized saline group, mean (SD) 71.68h (27.3) as compared with 57.7h (23.6) in normal saline group ( $P < 0.005$ ). Between the two groups, mean difference (95% CI) in functional duration of catheter was 13.9h (4.7 – 23.1) in favour of heparinized saline group. Kaplan-Meier survival estimate showed that at 90h of duration, 7 first cannula (10%) were patent in normal saline group compared with 17 first cannula (25%) in heparinized saline group ( $P < 0.001$ ).

The Centre for Clinical Effectiveness undertook a meta-analysis of results for catheter patency from Kumar et al (2013) and Upadhyay et al (2015). The definition of patency and functional duration used in both Kumar and Upadhyay refers to the duration of time the catheters were in place. The comparison of intermittent flushing studies was included in the meta-analysis. The pooled estimate of catheter patency from Kumar et al (2013) meta-analysis and Upadhyay et al (2015) RCT is shown in Figure 1. It indicates that for heparin usage as an intermittent flush solution, the pooled estimate showed a smaller benefit, mean difference = 3.88 hours (95% CI 0.23 to 7.52).

**Figure 1. Meta-analysis of data for catheter patency. IV, inverse variance. Heparin versus Saline (control).**



### Occlusion incidence

Upadhyay et al (2015) reported occlusion at catheter site as a secondary outcome and found it was the most common indication for catheter removal in both saline and heparinized groups (77.3% vs 71.7%). However this difference was not statistically significant.

### Line failure/infusion failure

Kumar et al (2013) found that when heparin was used in intermittent flush solutions the difference was not statistically significant (rate ratio: 0.88; 95% CI: 0.72–1.09;  $P = 0.25$ ) when compared with the placebo (saline).

### Phlebitis

Upadhyay et al (2015) reported phlebitis as the second most common cause of indication for catheter removal (28 and 22% in both saline and heparin groups).

In Kumar et al (2013) systematic review, they reported that the use of heparin showed lower rates of phlebitis, but this was not significant (rate ratio: 0.81; 95% CI: 0.47–1.41;  $P = 0.46$ ). Pooled effect size was statistically significant for the studies that provided data for multiple catheters per subject (5 studies; rate ratio: 0.61; 95% CI: 0.38–0.98;  $P = .04$ ).

### Adverse Events

No significant difference between groups for adverse events of heparin-induced thrombocytopenia (HIT) or sepsis were reported by Kumar et al (2013).

## Conclusions

In conclusion, this review of varied quality evidence found in favour of heparin for the reduction in incidence of IV blockages/catheter patency in paediatric populations requiring intermittent flushing of peripherally inserted lines. The results did not show any statistically significant benefit for heparin versus saline for outcomes related to occlusion incidence, line failure, phlebitis or other adverse events.

**Table 3. Summary of results**

| Paper                | Study Design      | Quality | Population   | Intervention   | Comparator  | Outcomes   | Results from outcomes of interest  |
|----------------------|-------------------|---------|--|--|---|--|--|
| Takashima et al 2015 | Scoping Review    | High    | All participant ages and settings (inpatient and ambulatory)   | Management of peripheral vascular devices  | Varied in the scoping search  | <ul style="list-style-type: none"> <li>catheter insertion strategies</li> <li>analgesia methods</li> <li>post-insertion care and maintenance, dressings</li> <li>securement</li> <li>flushing practices</li> <li>infection prevention strategies (i.e., skin preparation, hub decontamination)</li> </ul>  | 128 RCT's; only 2 relevant to our patient population (These are the below included papers)   |
| Upadhyay et al 2015  | RCT               | High    | Term and preterm neonates born at >32 weeks of gestation who require PIVC for intermittent administration of antibiotics | 1ml of heparinized saline (10Umn <sup>-1</sup> ) every 12 hours before and after intravenous antibiotics | Normal saline every 12 hours before and after intravenous antibiotics | <ul style="list-style-type: none"> <li>functional duration of first PIVC</li> <li>average catheter duration of any catheter inserted</li> <li>complications associated with PIVC including occlusion, phlebitis or infiltration, incidence of abnormal coagulation profile, allergic reaction to study medication, heparin induced thrombocytopenia</li> </ul> | <p><b>Mean functional duration</b> of first catheter was more in heparinized saline group, mean (SD 71.68h (27.3) as compared with 57.7h (23.6) in normal saline group (P&lt;0.005). Between the two groups, mean difference (95% CI) in functional duration of catheter was 13.9h (4.7 – 23.1) in favour of heparinized saline group. Kaplan-Meier survival estimate showed that at 90h of duration, 7 first cannula (10%) were patent in normal saline group compared with 17 first cannula (25%) in heparinized saline group (P&lt;0.001).</p> <p><b>Occlusion at catheter site</b> was commonest indication for catheter removal in both groups (77.3% vs 71.7%).</p> <p>Phlebitis was next most common cause of indication for catheter removal (28 and 22% in two groups).</p>   |
| Kumar et al 2013     | Systematic Review | High    | Pediatric  | Low-dose heparin   | Saline controls   | <p>Primary</p> <ul style="list-style-type: none"> <li>Duration of catheter patency</li> </ul> <p>Secondary</p> <ul style="list-style-type: none"> <li>Infusion failure</li> <li>Catheter-related phlebitis</li> <li>Adverse events reported</li> </ul>   | <p><b>Heparin usage as an intermittent flush solution</b></p> <ul style="list-style-type: none"> <li>Pooled estimate from the available RCTs showed a smaller benefit (mean difference: 2.82 hours; 95% CI: 20.04 to 5.67; P = .05), with no significant difference in effect size noted between the studies restricted to the neonatal population and the other studies. There was no significant heterogeneity noted in the estimates from these trials.</li> <li>The most common dose used in studies was 10 units/mL, although there was minimal additional benefit observed when this dosage was compared with the lower dosage, within-study design of 2 multigroup studies.</li> <li>Difference was not statistically significant when heparin was used in intermittent flush solutions (rate ratio: 0.88; 95% CI: 0.72–1.09; P = 0.25) compared with the placebo.</li> <li>The use of heparin showed lower rates of phlebitis, but this was not significant (rate ratio: 0.81; 95% CI: 0.47–1.41; P = 0.46)</li> <li>Pooled effect size was statistically significant for the studies that provided data for multiple catheters per subject (5 studies; rate ratio: 0.61; 95% CI: 0.38–0.98; P = .04).</li> <li>No significant difference between groups for adverse events (HIT, sepsis)</li> </ul> |

## References

- Bradford, N. K., Edwards, R. M., & Chan, R. J. (2015). Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children. *Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD010996.*
- Kumar, M et al. (2013). Low-Dosed Heparin Use and the Patency of Peripheral IV Catheters in Children: A Systematic Review. *Pediatrics*; 131:e864–e872.
- Takashima, M et al. (2015). Randomised controlled trials in peripheral vascular access catheters: a scoping review. *Vascular Access*, 10–37.
- Upadhyay, A et al. (2015). Heparin for prolonging peripheral intravenous catheter use in neonates: a randomised controlled trial. *Journal of Perinatology*: 35, 274-277.
- Arnts, IJJ et al. (2011). Effectiveness of heparin solution versus normal saline in maintaining patency of intravenous locks in neonates: a double blind randomized controlled study. *Journal of Advanced Nursing* 67(12), 2677–2685.

## Appendix 1

**Table 1.** Database search terms and results

| Database | Search terms   | Results                       |
|----------|--|-------------------------------|
| TRIP     | Heparin OR UH OR UFH OR LMWH AND Sodium Chloride OR Saline OR sodium* OR NaCl AND Catheterization, Peripheral OR Catheterization OR Catheters, Indwelling OR Vascular Access Devices OR catheter* OR cannula* OR extended peripheral cann* OR Peripherally Inserted Central Catheter Line Insertion OR PICC AND Paediatrics OR Pediatrics OR Child OR Adolescent   | 154 - With SR and 2012 filter |
| CINAHL   | Heparin OR (hep* or UH or UFH or LMWH) OR *parin OR *paran AND Sodium Chloride OR Saline Solution, Hypertonic OR saline OR sodium* OR NaCl AND Catheterization, Peripheral OR Catheterization OR Catheters, Indwelling OR Vascular Access Devices OR catheter* OR cannula* OR (extended peripheral cann* OR Peripherally Inserted Central Catheter Line Insertion OR PICC) AND Paediatrics OR Pediatrics OR Child OR Adolescent  | 45                            |
| Pubmed   | #1 MESH DESCRIPTOR Heparin EXPLODE ALL TREES<br>#2 (hep* or UH or UFH or LMWH):TI,AB<br>#3 *parin:TI,AB<br>#4 *paran:TI,AB<br>#5 #1 OR #2 OR #3 OR #4<br>#6 MESH DESCRIPTOR Sodium Chloride<br>#7 MESH DESCRIPTOR Saline Solution, Hypertonic<br>#8 saline:TI,AB<br>#9 sodium*:TI,AB<br>#10 NaCl:TI,AB<br>#11 #6 OR #7 OR #8 OR #9 OR #10<br>#12 #5 AND #11<br>#13 MESH DESCRIPTOR Catheterization, Peripheral<br>#14 MESH DESCRIPTOR Catheterization<br>#15 MESH DESCRIPTOR Catheters, Indwelling<br>#16 MESH DESCRIPTOR Vascular Access Devices<br>#17 catheter*:TI,AB<br>#18 cannula*:TI,AB<br>#19 PICC:TI,AB<br>#20 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19<br>#22 #12 AND #20<br>#23 MESH DESCRIPTOR Paediatrics<br>#24 MESH DESCRIPTOR Pediatrics<br>#25 MESH DESCRIPTOR Child<br>#26 MESH DESCRIPTOR Adolescent<br>#27 #23 AND #24 AND #25 AND #26<br>#28 #22 AND #27 | 350                           |