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Effects of Intravenous Iron Infusion Frequency, Duration, and Safety on Quality of Life: Results of a Time Trade-Off Study in Patients with Iron Deficiency Anemia in China

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Background

Intravenous (IV) iron is the preferred and most efficacious treatment for patients with iron deficiency anemia (IDA) when oral iron cannot be used or where rapid iron delivery is required; however, IV infusions are invasive and require patients to be hospitalized or travel to specialist infusion units, which can have a detrimental effect on quality of life. The required number and duration of infusions varies between IV iron formulations; for instance, ferric derisomaltose can be dosed up to 20 mg of iron per kilogram of bodyweight, maximum single doses of ferric carboxymaltose and iron sucrose are limited to 1,000 mg and 200 mg of iron, respectively.

The aim of the present study was to elicit health state utility values (HSUVs) pertaining to the administration of IV iron from a population of patients with IDA in China, and to compare the results with a previous study conducted in the general population.[1]

Methods

A time trade-off (TTO) study was designed with seven health states covering different numbers of IV infusions of the same duration (either 1, 2, 5, or 7 infusions), different durations of infusion (15-30 minutes versus 30-60 minutes) and risk of long-term side effects of the infusion (Figure 1). To ensure that the vignettes describing the health states were accurate and reflected patient experience, the disease and health state descriptions were developed from the literature, summaries of product characteristics, and patient leaflets. Absolute HSUVs were compared with a previous study conducted in the general population in China.[1]

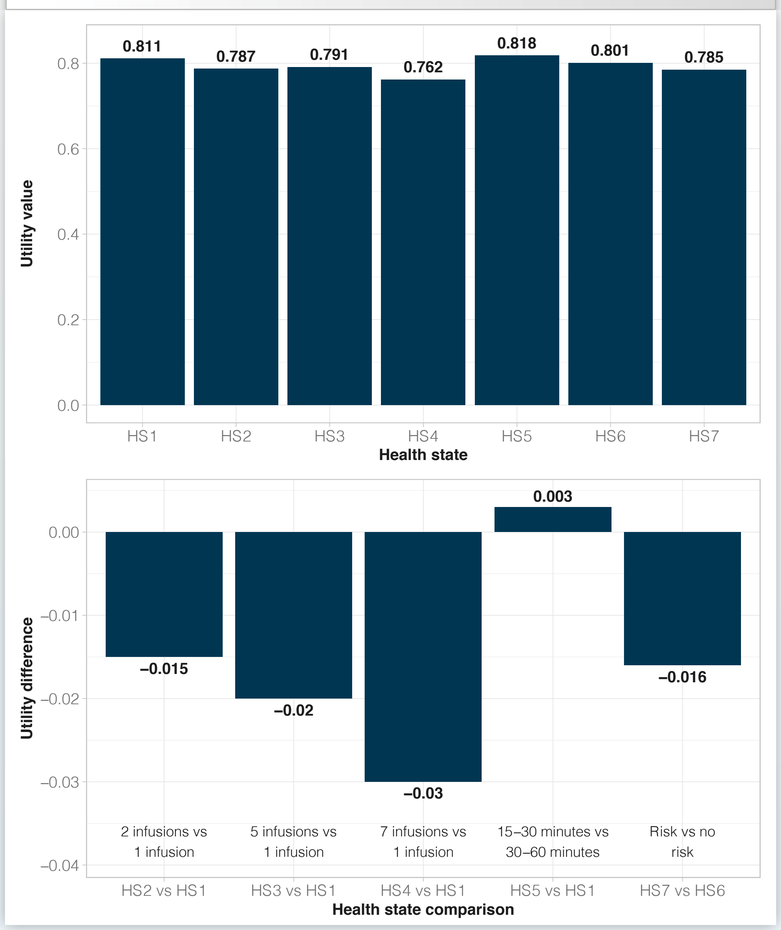
Utility values were calculated for each health state, with standard errors and 95% confidence intervals (CIs) obtained from non-parametric bootstrapping based on 10,000 iterations. Disutilities between states were calculated as the difference between utility values after the removal of outliers (2.5% at the bottom and top of the utility distribution) to increase the reliability of results. Analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

The number of vignettes presented was limited to avoid overburdening respondents. In the present survey, this meant that only one, two, five, and seven annual administrations could be investigated, for infusions with a duration of 30–60 minutes and no risk of hypophosphatemic osteomalacia (HS1–4). For cost-utility analyses, however, additional flexibility to model a variable number of infusions is often desirable. This flexibility was achieved by implementing a diminishing marginal disutility model (DMDM), based on work by Lauridsen *et al.* for hypoglycemia.[2] Using this model rested on the assumption that, as for hypoglycemic events, the "first is the worst" for IV iron infusions – each additional infusion will reduce utility but by a smaller amount than the preceding infusion.

Results

A total of 816 patients were recruited, of whom 58% (n=476) ultimately met the inclusion criteria, succesfully completed the TTO test question, and completed the whole survey. Of the 476 patients ultimately included in the analysis, 23% were male and 77% were female, and 29% had previously received an IV iron infusion. The most common reason for administration of exogenous iron (either oral or IV) was surgery, followed by gastrointestinal disease, and heavy uterine bleeding. The median number of infusions received by patients in the IV iron group in the past year was 3, and the median time since the last IV iron infusion was 2 months. Patients had been receiving IV iron infusions for up to 10 years with a median duration of IV iron treatment of 2 years.

Figure 2. Mean health state utility values (top) and disutilities between states (bottom)



Patients with IDA reported that 1, 4, and 6 additional IV infusions would result in disutilities of 0.015 (p=0.005), 0.020 (p<0.001), and 0.030 (p<0.001), respectively (FIgure 2). The risk of long-term side effects was associated with a disutility of 0.016 (p=0.002) while the difference from reducing the time needed for infusion from 30-60 minutes down to 15-30 minutes was not significant (p=0.805). Absolute HSUVs were consistently higher in the IV iron population, than in the prior general population study, but differences between states were broadly consistent.

The diminishing marginal disutility model developed to calculate the disutilities associated with additional infusions with a duration of 30–60 minutes and no risk of hypophosphatemic osteomalacia had the functional form $U_d=0.0145\times x^{0.341}$ (Figure 3). For instance, three IV iron infusions per year, each with a duration of 30–60 minutes and without risk of hypophosphatemic osteomalacia, would be associated with an annual utility decrement of 0.021 relative to no such infusion in a year. Fifteen such infusions would be associated with an annual disutility of 0.037 relative to no such infusion in a year.

This function allowed the derivation of disutilities for administration frequencies not directly covered in the TTO survey, and yielded lower disutility estimates relative to equivalent models developed based on the general population (Figure 3). For instance, three IV iron infusions per year, each with a duration of 30–60 minutes and without risk of hypophosphatemic osteomalacia, would be associated with an annual utility decrement of 0.021 relative to no such infusions in a year. Fifteen such infusions would be associated with an annual disutility of 0.037 relative to no such infusion in a year.

Marginal disutilities derived from the power model indicated that, as the number of additional infusions increased, utility continuously decreased but at a diminishing rate (Figure 3). Receiving one 30–60 minute infusion without risk of hypophosphatemic osteomalacia, relative to receiving no such infusion reduced the annual utility by 0.0145, while going from four to five infusions reduced utility by 0.0018, and going from fourteen to fifteen infusions further reduced utility by 0.0008.

Conclusion

- The present TTO study demonstrated that more infusions and risk of long-term side effects have a significant impact on quality of life in patients with IDA.
- These results from an IDA population were closely aligned with those elicited from the general population.

Figure 3. Comparison of power models fit to time trade-off results for an additional one, four, and six infusions (versus one infusion) in the general population versus a population who had received intravenous iron infusions

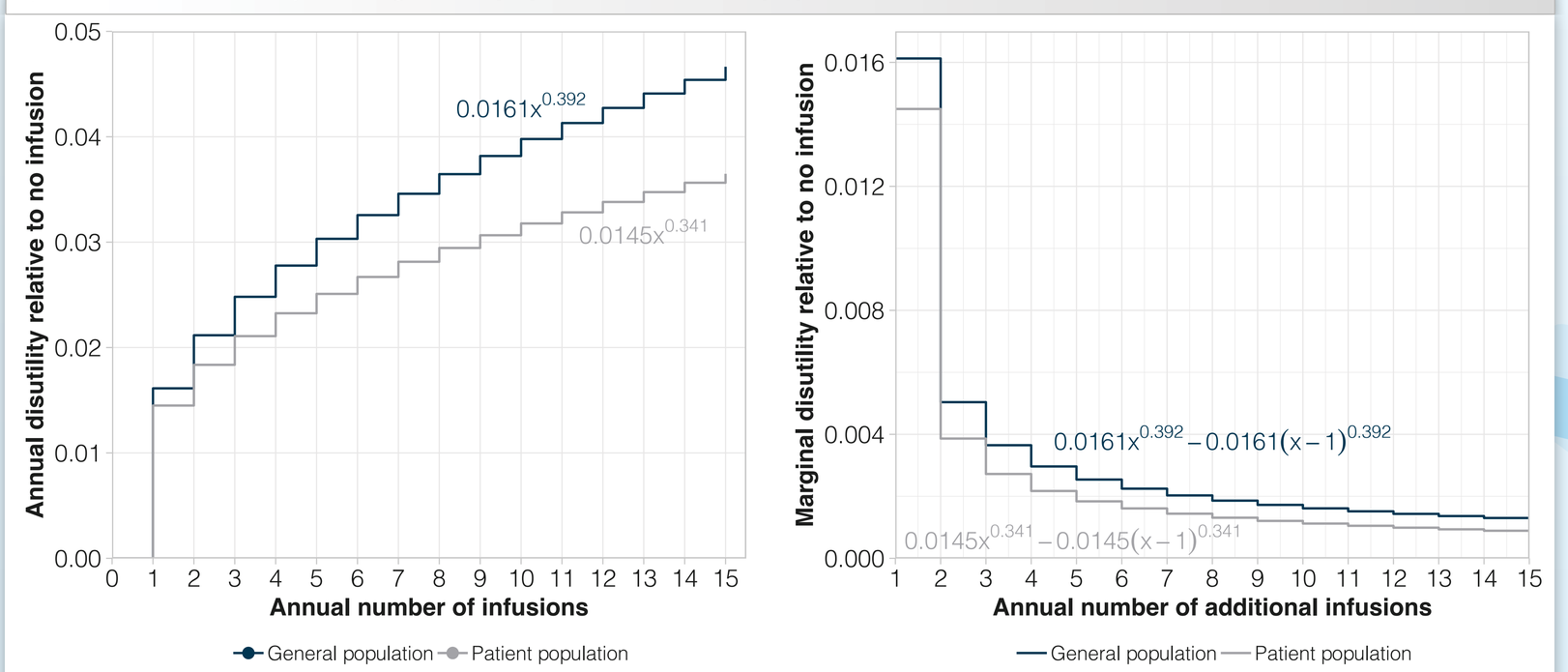


Figure 1. Summary of the seven health states included in the time trade-off study differentiated with regard to the duration, frequency and risk profile of intravenous iron infusions

	HS 1	HS 2	HS 3	HS 4	HS 5	HS 6	HS 7
Infusion frequency	1	2	5	7	1	2	2
Infusion duration	30-60 min	30-60 min	30-60 min	30-60 min	15-30 min	15-30 min	15-30 min
Long-term side effects	No risk	No risk	No risk	No risk	No risk	No risk	Risk

References

1. Wu D, Zhang Y, Boegelund M, Pollock RF, Hu S. Development of a Diminishing Marginal Disutility Model for Intravenous Iron Infusions Based on Data from a Time Trade-Off Study in China. Abstract and poster presentation POSA319 at Virtual ISPOR Europe 2021. 30 November – 3 December, 2021.
2. Lauridsen JT, Lønborg J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. Qual Life Res. 2014;23(9):2645-50.

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